BRITISH SURGICAL PRACTICE

SURGICAL PROGRESS 1960

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1960

Under the General Editorship of
The Late SIR ERNEST ROCK CARLING
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and
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PUBLISHERS' ANNOUNCEMENT

THIS 1960 *Progress Volume* is the tenth of an annual series of supplements to *British Surgical Practice*. By this means the eight volumes of the main work are kept up to date in the ever increasing field of surgical knowledge, by original articles, critical surveys and abstracts.

The Noter-up section will guide the reader from the main work to the supplementary material which appears in this or previous Progress Volumes. The purpose of the Noter-up remains the same as in previous years. The reader should first of all refer to the material in the main volumes of *British Surgical Practice*. Then, in order to ascertain the advances and changes which have been discussed in this or previous Progress volumes, he should refer, under the same heading or key number as that consulted in the main work, to the Noter-up in the latest Progress Volume. There he will find details of the articles, surveys and abstracts relating to the subject which have appeared in the Progress Volumes. Regional or system surveys naturally cover a wider field than in previous volumes and individually apply to more than one chapter in *British Surgical Practice*. Because of this, the main subject headings within the surveys have been linked in the Noter-up to the appropriate chapter titles of the main work. Thus by reference to the Noter-up, the reader of the main volumes is easily able to locate any new material on a particular subject even though it may be contained within a survey. The nature of surgical advance has necessitated the inclusion of new titles in the Noter-up, and for convenience and ease of reference, these are as follow: Abdomen; Anal Diseases; Antibiotics; Brain—Psychiatric Disorders; Brain—Vascular Anomalies; Cancer; Carcinoid; Carpal Tunnel Syndrome; Collagen Diseases; Electronics; Fluid and Electrolyte Balance; Genetics; Gynaecology; Kidney and Ureter—Nephrectomy; Kidney and Ureter—Surgical Aspects; Liver—Surgery; Lung—Surgery; Obstetrics; Organ Transplantation; Pelvic Organs—Viscerectomy; Pituitary Gland; Plastic Surgery—Correction of Facial Deformity; Thorax—Congenital Deformities; Ureter—Replacement of; Virus Diseases.

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CONTENTS

Non-subscribers will find the Noter-up section of value in that it is alphabetically arranged and gives at a glance information as to the presence or absence of recent material on any particular subject. Consequently, the book can be used independently.

Errata to 1959 *Progress Volume*

Page 119, legend to Fig. 37: the first two lines should read "Same patient as Fig. 29 after radical parotidectomy."

Page 221, Fig. 50: The vertical lines showing the standard error of the mean survival at each age period were finally omitted from this diagram as the figures were calculated from the data collected by only one of the three observers (Greenwood).

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SURGICAL PROGRESS, 1960

THIS VOLUME IS AN ESSENTIAL PART OF YOUR SET OF
BRITISH SURGICAL PRACTICE

1. Every article in the main volumes of *British Surgical Practice* has a Key Number, which appears at the commencement of each article and also at the top left-hand corner of the right-hand pages.
2. To ascertain whether there has been any recent advance in any subject to which reference is being made, the reader should merely turn to the appropriate Key Number in the outer margin of the "Noter-up" Section appearing at the end of the book.
3. He will there find either a note that no further references appear or information as to the type and content of new matter, year of publication and page number.

INTRODUCTION

It is now some time since the Editors of British Surgical Practice warned the Publishers that if the work was to continue it would have to be done by younger men. This suggestion was sympathetically received and arrangements to continue the work in a somewhat modified form were almost complete when, with tragic suddenness, Sir Ernest Rock Carling died. His mind was so active and his interest in current affairs was so intense that we forgot his age, and his departing was a shock to his many friends and associates.

He had borne more than his fair share of the burden of collecting the material for the present volume, and had read most of the proofs. And as contributions have to be planned far in advance it is good to know that next year's volume will be influenced by his lively appreciation of the dependence of surgery upon recent developments in biological science.

The contents of this volume conform to the pattern set in recent years in that there are some articles which bring those of the original work up to date; some deal with subjects which have been worked out since the publication of the original volumes and are in this sense among the more recent developments in surgery; and there are others which indicate the lines which future surgical progress may be expected to follow.

In the first category are the contributions by Mr. Harrold on acute infective arthritis; on primary Raynaud's disease by Mr. Peacock who elaborates the endocrine aspects of this malady and thus places its treatment on a more rational basis; by Mr. Plewes whose article on fractures is full of practical advice, the harvest of a rich and varied experience; by Mr. Hanley who shows how chemotherapy and conservative surgery can sometimes save at least part of a tuberculous kidney; and by Mr. Dee Shapland who brings up to date the treatment of retinal detachment.

In the second group there is a review of carcinoid tumours by Mr. Davies; a paper by Mr. Drew on the use of profound hypothermia in heart surgery; an article by Mr. Hankey and Mr. Ellison Nash on the common but often misunderstood disorders of the temporo-mandibular joint; and the account of islet-cell lesions of the pancreas by Dr. MacKenzie and Dr. Friedman which is doubly welcome because of its importance and its Canadian authorship. This group also includes Mr. Mogg's review of the urinary complications of spinal cord malformations, conditions once regarded as hopeless but now responding reasonably well to the devoted efforts of surgeons, nurses, physiotherapists and parents.

The remaining articles, though not easy to read, should be carefully studied by any surgeon who is seeking to understand current opinion about the processes of normal and abnormal tissue growth, based upon genetics and immunology as well as upon infecting agents like viruses. We are

ACUTE INFECTIVE ARTHRITIS

By A. J. HARROLD, M.S., F.R.C.S.

Consultant Orthopaedic Surgeon, St. Mary's Hospital, and Paddington General Hospital, London

Acute arthritis caused by an infective agent in the joint tissues has become uncommon. The following article reviews present knowledge on the pathology, diagnosis, treatment and complications.

AETIOLOGY

Infection reaches a joint by any of three routes, by blood spread from a distant focus, by direct spread from a local bone or soft tissue lesion, or through an open wound.

Haematogenous infection is the most common and the most important in diagnosis and treatment. The unqualified term acute infective arthritis usually implies blood-borne infection. It occurs at any age, but particularly in children, especially the newborn. Any joint may be involved but the hip, knee, elbow, shoulder and ankle are the most common. The organisms may be derived from an infected umbilicus, respiratory tract, middle ear or skin lesion. An obvious primary focus has been reported in from 100 per cent (Nicholson, 1949) to none (Heymann and his colleagues, 1953) of the patients, a wide range which reflects the wide variations in the clinical picture. A history of antecedent closed injury to the joint is occasionally obtained. The writer knows of two cases in which infective arthritis complicated recurrent internal derangement of the knee.

Spread of infection from acute osteomyelitis is possible where the joint capsule is attached to the bone on the diaphyseal side of the epiphyseal line, as at both ends of the femur and humerus and at the upper end of the ulna and radius. At the upper end of the femur, in particular, it is estimated that osteomyelitis is complicated by septic arthritis in 60–90 per cent of cases (Hutter, 1948; Blanche, 1952). The combined lesion produces a more severe illness than either alone.

In contrast, infection of a joint by direct implantation through a wound leads usually to only a mild systemic disturbance although the possibilities for local damage are still considerable.

Over the past few years a new aetiological factor has been introduced, namely, diminished resistance to infection after the administration of corticosteroids. The hazard of introducing infection with an intra-articular injection is referred to later.

therefore very grateful to Dr. Stevenson, to Dr. Humble and Dr. Newton, to Dr. Loutit and also to Professor Dick and Dr. Dane for responding to our request to interpret their scientific specialties to surgeons. Mr. Dempster's contribution is a valuable sequel to the article he wrote for the 1955 volume on Organ Transplantation, and describes some of the problems which arise in the practical application of the more theoretical and experimental aspects of tissue grafting. Finally we are indebted to Mr. Reginald Vick for an admirable account of the organization of a Cancer Records Bureau and the use that can be made of the information thus obtained as a guide to the treatment and prognosis of cancer in various sites.

Throughout our happy association as Editors of British Surgical Practice we have been deeply appreciative of the kindly and understanding cooperation of the many friends whom we have invited to write for us, and I know I am doing only what Sir Ernest would have wished when I offer our grateful thanks to all who have helped with the present volume.

J. PATERSON ROSS

of mumps (Applebaum and his colleagues, 1952), it is doubtful whether the joint symptoms are caused by the actual presence of the infecting agent. It seems more probable that the arthritis is the result of an incompletely understood antigen-antibody reaction, such as is postulated in the clinically similar rheumatic fever and serum sickness. It is probable that the arthritis occurring in ulcerative colitis is of the same nature.

MORBID ANATOMY

The infecting organisms lodge in the synovial membrane. They do not appear in the synovial fluid unless the infective focus ulcerates into the joint cavity. Organisms introduced into the joint by a wound tend to be picked up by the synovial membrane in the same way as other particulate matter loose in the joint. For these reasons failure to recover the organism from the joint effusion is common, occurring in up to 50 per cent of otherwise typical cases of infective arthritis.

In such illnesses as pneumonia, subclinical infection of joints with rapid resolution of the inflammation may be much more common than is generally supposed (Collins, 1949).

In established infection the synovial membrane shows all the changes associated with the classical account of the inflammatory process. It becomes intensely congested and swollen and areas of superficial necrosis may be evident. The periarticular structures are involved and become oedematous. An inflammatory exudate accumulates in the joint cavity, forming an effusion, the nature of which varies with the organism, the stage of the disease and the effects of treatment. In staphylococcal arthritis it rapidly becomes frankly purulent and perhaps blood-stained. Cocci may be visible on microscopic examination of a smear. The effusion becomes thinner and clearer with resolution of the inflammation. Flakes of fibrin are a feature in some infections and then render aspiration difficult. In favourable circumstances the inflammatory process in the synovial membrane and periarticular structures resolves completely. More often, organization of exudate in the synovial recesses of the joint and between the periarticular structures produces adhesions, both intra-articular and extra-articular, which limit joint movement for a time, sometimes permanently.

The most serious effect of suppurative arthritis is on the articular cartilage, a tissue with very limited powers of regeneration (Fig. 1). Phemister (1924) described how the articular cartilage is destroyed, the damage occurring first and most severely over the points of pressure. The whole thickness may be lost in a matter of days. He attributed this cartilage destruction to the action of proteolytic enzymes derived from the leucocytes. Lack (1959) has recently drawn attention to a much more potent source of protease. Many strains of staphylococci and streptococci produce kinases, direct or indirect activators of plasmin, the natural protease of the blood. Plasminogen, the enzyme precursor, enters the joint with the inflammatory exudate. In the presence of staphylokinase or of streptokinase, it is converted to the active enzyme which attacks the ground substance of cartilage, liberating the chondroitin sulphate from the protein moiety (Lack and Rogers, 1958). Reconstitution of the ground substance is prevented by the lethal effect of the bacterial toxins on the cartilage cells.

When infective arthritis complicates orally-given steroid therapy the symptoms and signs are profoundly depressed and diagnosis may be long delayed (Mills and his colleagues, 1957). Fortunately such an occurrence is rare.

BACTERIOLOGY

The organism most frequently recovered is the *Staphylococcus aureus*. Watkins, Samilson and Winters (1956), reporting on patients treated between 1934 and 1955, found staphylococci in 35 per cent. Present experience is that they are responsible in more than two out of every three cases. Staphylococcal arthritis is particularly destructive, and is often secondary to osteomyelitis.

Streptococcal infection, which used to be common in infants, is now relatively unusual. It occurred in only eight per cent of the infants reported by Blanche (1952). This may be because of the more efficient treatment of primary streptococcal infections, but is also, perhaps, part of the apparent general decline in virulence of the organism.

Pneumococci, meningococci, *Bacillus coli*, *Salmonella typhi*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Proteus vulgaris* have all caused infective arthritis without special feature. Gas formation has been noted in *B. coli* arthritis (Miller and Engle, 1951).

The transient arthralgia of undulant fever must be distinguished from true brucellar arthritis in which the organisms may be recovered from the joint effusion (Makin, Alkalaj and Rozansky, 1957). The agglutination reactions are valuable here in diagnosis and may be positive in the synovial fluid earlier than in the serum.

Gonococcal arthritis, proved by culture of the organism from the joint, is now very rare. Such infection is apt to be severe with extensive joint destruction and suppuration. Much more common is a form of arthritis which has been attributed to gonorrhoea on circumstantial evidence alone, evidence which has recently been severely criticized (Harkness, 1949; Ford, 1953). An acute, febrile, migrating polyarthritis, affecting particularly the joints of the lower limbs, follows an attack of gonorrhoea. The urethral discharge sometimes accompanies the arthritis and there may also be conjunctivitis or iritis. The disease is self-limiting, but recurrent or chronic arthritis may lead to permanent joint damage, especially in the feet. Ankylosing spondylitis is an occasional sequel. Treatment by antibiotics is ineffective, although gonococci are normally among the organisms most susceptible to penicillin. The clinical pattern is identical with that of the arthritis that may follow non-specific urethritis. In the case described by Reiter (1916), when he gave his name to this triad of arthritis, urethritis and conjunctivitis, the symptoms followed bacillary dysentery. It is now suggested that this syndrome is caused by an entirely different infective agent, perhaps the pleuro-pneumonia-like organism which may be found in the urethral discharge, or a virus. The infection is contracted either as a venereal disease, or in association with dysentery, or sometimes from no obvious source.

Acute arthritis associated with leptospiral infection has been described (Sutliff, Shepard and Dunham, 1953), but, as with that which may follow closely an attack

condition not infrequent in the small joints of the fingers and toes following a wound or ulcer. In the major joints continued muscle spasm leads to secondary deformity.

The inflammation may, in the hip, cause thrombosis in the vessels supplying the femoral head epiphysis which then dies, and, if infected, forms a sequestrum. If the dead epiphysis is not itself infected revascularization is possible. The temporary disappearance of an ossific centre in the radiographs (Fig. 2) occasionally seen in infants, may be attributed to such an episode of necrosis followed by revascularization (Nicholson, 1949; Siffert, 1957).



FIG. 2.—Apparent destruction of the epiphysis in the lateral femoral condyle. Radiographs taken one year after a neonatal infective arthritis. Full recovery is the rule. (*Case of Mr. G. C. Lloyd-Roberts.*)

In infants, the entire upper end of whose femur is cartilaginous, digestion of this cartilage leads to loss of the head and much of the neck of the femur, producing an apparent dislocation. True dislocation of the hip results from extreme distension of the joint capsule by the effusion and from destructive changes in the acetabulum. The flexed, adducted position sometimes assumed predisposes to dislocation.

In contrast, joint infection by an organism that does not produce a kinase, although associated with a purulent effusion, often leads to little or no appreciable damage to the articular cartilage.

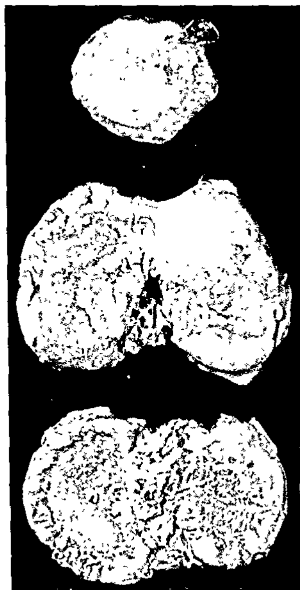


FIG. 1.—The joint surfaces in staphylococcal arthritis after meniscectomy. Severe destruction of the articular cartilage is shown, and is particularly evident at the points of pressure. (*Specimen from Dr. C. H. Lack.*)

Slight damage to the articular cartilage is followed in time by osteoarthritis. Complete loss produces ankylosis, often fibrous but more typically by bone.

If the infection is not overcome it spreads to the bone, producing an osteitis with cartilage and bone sequestra. The effusion bursts through the joint capsule, tracks to the skin and forms a sinus. Chronic suppurative arthritis results, a

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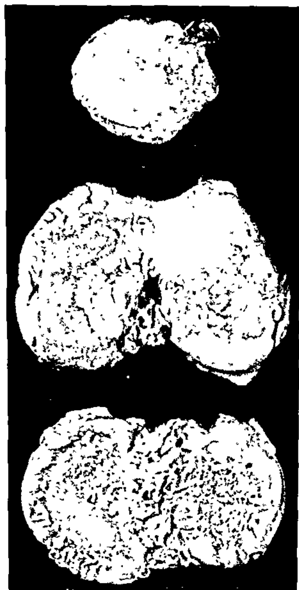


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Rheumatic fever

The history of recent infection in the tonsils and the sudden onset of pain in a joint and fever may suggest infective arthritis. The joint becomes warm and tender and shows limitation of all movement. Swelling is, however, slight or absent. Signs of rheumatic carditis may be present. Typically the joint symptoms are transient but multiple, affecting several of the larger joints in turn. The arthritis may, however, be monarticular for as long as five days and, when associated, as it may be, with a raised white cell count and high fever, it may be difficult to distinguish from acute osteomyelitis or suppurative arthritis.

Haemarthrosis

Spontaneous bleeding into a joint occurs in haemophilia, from joint angiomas, and, rarely, from trivial injury in an apparently normal or osteoarthritic joint. The pain and swelling develop more rapidly than in infective arthritis, becoming severe in one or two hours. Limitation of joint movement is pronounced and there is increased local heat. The effusion is often tense. The synovial membrane is, however, not diffusely tender, a point of value in distinguishing a post-operative haemarthrosis from an infected effusion. A mild systemic disturbance with a pyrexia up to 100°F. occurs.

Transient synovitis

Pain in the hip, of apparently spontaneous onset, is quite often seen in children. Limitation of movement is equal in all directions and may be pronounced. Local tenderness, however, is slight, there is no pyrexia and the results of investigations are normal. With rest the condition subsides in a few days.

Gout

Gout gives rise to an acute arthritis most often seen in the metatarso-phalangeal joint of the big toe but sometimes occurring in the larger and more central joints. It is very uncommon in women and is rare in men before the age of 30 years. Since the inflammation arises in the urate deposits in the periarticular tissues, swelling and extreme tenderness of these tissues are the cardinal features. The inflammation often spreads to the skin, which becomes red, glazed and oedematous. At the height of the attack all movement is prohibited by pain. Pyrexia of 101°–103°F. and leucocytosis are common. A cloudy joint effusion forms. The attacks tend to be recurrent. Tophi may be present. The serum uric acid is raised, but undue reliance should not be placed on a single estimation as the level is apt to fall with the onset of acute symptoms. The diagnosis is confirmed by therapeutic test. Colchicine provides specific relief in 80 per cent of cases. A dose of 0·5 milligram is given every two hours until pain is relieved or vomiting and diarrhoea develop.

INVESTIGATIONS

Radiology

Radiographs during the early stages may show, in the soft-tissue shadows, distension of the joint capsule. In infancy a large hip effusion causes lateral displacement of the whole upper end of the femur (Fig. 3). In arthritis secondary to osteomyelitis local bone erosion and subperiosteal new bone becomes visible two to three weeks

CLINICAL FEATURES

The clinical features of acute infective arthritis vary widely and are particularly affected by the age of the patient.

Typically, over some 12–36 hours the affected joint becomes painful and swollen. There is general malaise and fever, commonly reaching 102°–103°F. The use of the limb is lost, and there is increased local heat over the joint. All movements are equally restricted by pain. In the early stages only the extremes of motion are lost with a relatively painless range in between. Later, the least movement is exquisitely painful, the joint, on attempted examination, being held immobile by muscle spasm. It lies in the position of greatest capacity—for example, in the knee some 20 degrees short of full extension, in the hip in slight abduction, flexion and external rotation. The joint cavity is distended by an effusion, often tense. The synovial membrane becomes diffusely tender.

A primary focus of infection may be evident. Occasionally the local symptoms are masked by those of an overwhelming septicaemia. Delirium and coma, with loss of use of a limb may mimic meningitis or the early stages of poliomyelitis.

Infection of two or more joints at one time occurs in about one of ten cases. It is relatively more common in infancy.

The classical picture of an acutely inflamed joint is not usually seen in the newborn, an age when joint infections are particularly common. Systemic features, pyrexia and disturbance of general health are slight. Swelling of the joint occurs, but, when deep-seated as in the hip, may readily be overlooked. A cardinal sign at this age is decreased active and passive movement in the affected limb. The sudden onset of restricted joint movement and muscle spasm in an infant should always suggest infective arthritis.

The naturally quiet progress of joint infection in infancy may be further obscured by the effect of antibiotics quite legitimately given for the treatment of the primary infection elsewhere in the body. The diagnosis may not become evident until an abscess presents, or a limp from a dislocated hip is noticed during convalescence.

A similar absence of systemic features occurs in the aged (Blatchford, 1953), where the sudden onset of uselessness in a limb may be ascribed to a "stroke", from a cerebrovascular accident.

DIFFERENTIAL DIAGNOSIS

Acute osteomyelitis

Although there are pain, swelling and tenderness at a joint in acute osteomyelitis, close examination shows these features to be greatest at the bony metaphysis and not over the synovial sac. A clear sterile effusion often develops but remains small. Limitation of joint movement is attributable to tension in the inflamed periosteum and is not pronounced. Suppurative arthritis may coincide with, or follow, osteomyelitis, in which event there will be a greater loss of movement, a large effusion, and tenderness not only over the bone but over the whole synovial sac.

Cellulitis and bursitis

Cellulitis and bursitis adjacent to a joint are not associated with tenderness of the whole synovial sac, nor is joint movement limited equally in all directions.

Serological tests are of value in brucellar, typhoid and gonococcal arthritis and in certain subacute and chronic types of staphylococcal arthritis (Lack, 1957).

Joint aspiration

In acute infective arthritis the diagnosis is confirmed and treatment started by aspirating the joint. The joint must be explored with a needle without delay



Fig. 4.—Acute infective arthritis of the hip. The joint space is obliterated and there is bone erosion from secondary osteitis of the femoral head epiphysis. (*By courtesy of Dr. F. Campbell Golding.*)

whenever the possibility of acute infection arises. This simple procedure sometimes gives rise to unnecessary difficulties. The following points should be observed.

after the onset of the disease. Radiographs also serve to exclude fractures, epiphyseal injuries and long-standing bone infection. They give important information as the disease progresses on the extent of damage to the articular cartilage. In the late stages diffuse osteoporosis of all the related bones must be distinguished from the bone erosion of secondary osteitis (Fig. 4).



Fig. 3.—Acute osteomyelitis with septic arthritis of the hip in infancy. Lateral displacement of the whole upper end of the femur and subperiosteal new bone are shown. (*By courtesy of Dr. F. Campbell Golding.*)

Haematological and serological investigation

The white blood cell count and the erythrocyte sedimentation rate are usually raised in proportion to the severity of the systemic illness. The responsible organism may, in the early stages of the disease, be recovered by blood culture.

joint. The decreased resistance to infection induced by the corticosteroids renders asepsis more than ever important when these drugs are being used. Adequately sterilized syringes are essential. Autoclaving or dry heat are safe methods. At open operation a non-touch technique and adequate skin towelling present undeniable advantages.

Treatment of established infection

The treatment of acute infection in a joint is based on the same principles as those for localized infection elsewhere. Difficulties have arisen when these principles have been ignored in a misguided attempt to keep the joint moving. The preservation of joint movement is best served by treatment aimed to overcome the infection swiftly. The inflamed tissues are put at rest by splinting. Antibiotics and supportive measures are used. The inflammatory exudate is removed to relieve tension, to take away harmful products and to promote the inflow of antibodies.

Splinting

The joint is immobilized to relieve pain, to assist resolution of the inflammation, and to prevent deformity. It is customary to splint the joint in the best position for ankylosis, should this occur. Traction is theoretically advantageous because articular cartilage is particularly liable to damage at points of pressure (Phemister, 1924). A moderate pull should be applied especially in the early stages of the disease. Any splint used should allow ready access to the joint for examination and aspiration.

In practice, the foot and ankle joints are conveniently immobilized in a plaster of Paris back splint, the foot being neither inverted nor everted, and the ankle at a right angle. The knee is immobilized 10–15 degrees short of full extension on a plaster slab, or better, in a Thomas' knee splint with skin traction. Balanced skin traction on the leg will relieve pain and facilitate nursing in arthritis of the hip. Full immobilization of the joint in plaster is needed only if it becomes apparent that the joint is seriously damaged. Immobilization in 30 degrees flexion, 5 degrees abduction and neutral rotation is then indicated. The wrist should be immobilized in 20 degrees extension, care being taken that the plaster allows free finger movement. The elbow and shoulder are conveniently rested in a sling, but if shoulder ankylosis seems probable 30–40 degrees abduction and rather less internal rotation should be obtained by suitably placed pillows, plaster, or an abduction splint. Splinting is continued until the local signs of inflammation have subsided. Progressive active movements are then important.

Antibiotics and chemotherapy

Orally given sulphonamides appear in the joint effusion in a concentration about two-thirds of that in the blood, which is a satisfactory therapeutic level (Blaisdell and Harman, 1942). Parenteral penicillin G produces levels approximately proportional to the dose used, but considerable individual variation occurs (Florey and his colleagues, 1949). Jocson (1955) found that procaine penicillin, streptomycin, the tetracyclines and chloramphenicol appeared in the joint fluid in very low concentrations, if at all. However, Linsell and Fletcher (1950) reported an effective level of oxytetracycline in the joint fluid of one case of Reiter's syndrome.

Technique

A general anaesthetic is indicated if the joint is already so tender that finger pressure cannot be tolerated. It is also often indicated when the joint concerned is deeply placed, as with the hip, especially in children. Otherwise the skin and peri-articular tissues are infiltrated with local anaesthetic before the passage of an aspirating needle or trocar and cannula of sufficient calibre (size 1 intramuscular needle or larger). Full aseptic precautions are taken.

The knee is entered at the level of the upper border of the patella, the needle point being aimed to lie between the patella and femur. The ankle is best approached from the front, the wrist from the dorsum, and the elbow from the outer side, over the radio-humeral joint. A needle inserted directly backwards from a point one inch in front of the acromio-clavicular joint will enter the shoulder. The many approaches to the hip suggest that none is particularly easy. The simplest and shortest is from the front. The hip joint lies just below and lateral to the midpoint of the inguinal ligament. A needle passed directly backwards from this spot, avoiding the femoral vessels, will strike the femoral head within the joint. The effusion will often flow out under pressure. A stilette should be available to clear the needle should it become blocked. Moving the tip of the needle and gentle manual pressure will assist in evacuating the joint.

All the effusion should be taken off. If cloudy or purulent, penicillin and streptomycin (250,000 units and 1 gramme respectively dissolved in 5 millilitres sterile distilled water for the adult) are injected into the joint before removing the needle. The aspirated fluid is examined for cells and organisms. Organisms are also sought by culture and tested for their sensitivity to the various antibiotics.

TREATMENT

Prophylactic treatment

Open wounds of joints and compound fractures that communicate with a joint must be subjected to a meticulous cleansing and débridement. Penicillin and streptomycin in solution should be left inside the joint. In favourable circumstances the wound is closed in layers, a splint applied and prophylactic antibiotics given until healing is complete. When contamination has been severe, or surgical treatment delayed, complete closure of the wound is contra-indicated. The synovial membrane or joint capsule should alone be sutured while the superficial layers are lightly packed open with gauze. Closure of the skin by suture or graft is carried out three or four days later, provided no gross infection has developed. Healing by granulation should be avoided wherever possible, since serious loss of movement may result.

In the case of small puncture wounds, common in the knee, provided there is no retained foreign body, treatment is expectant. Antitetanus serum or toxoid is given as indicated. The joint is rested and kept under close observation. Prophylactic antibiotics are not usually indicated. Evidence of infection may be expected within a week of the injury, often within two days. Treatment should be started promptly if pain or an effusion or a raised temperature develop.

Infection still occurs as a complication of therapeutic injection and surgical operations. Full aseptic ritual should be used when aspirating or injecting into a

and children dislocation of the hip is more common in those cases treated by aspiration than in those treated by incision and drainage (Samilson, Bessani and Watkins, 1958). Smith (1951) pointed out that incision and drainage alone, in pre-antibiotic days, used often to be sufficient to save the joint. In general, scarring around the hip interferes less with joint movement than it does around the knee or elbow. In the hip, therefore, the indications for incision and drainage are stronger, and the objections weaker than in the more superficial joints. Treatment by aspiration remains the method of choice when the diagnosis is early, the effusion thin and toxaemia mild. If these conditions are not met, open arthrotomy and the insertion of a drain down to, but not inside, the joint is indicated. Drainage should be dependent.

PROGNOSIS

The prognosis is influenced by the nature of the infecting organism, the particular joint involved, the presence of primary or secondary osteomyelitis, and the interval between the start of the disease and effective treatment. Staphylococcal and streptococcal infection, for example, are particularly likely to destroy the articular cartilage. The anatomy of the hip joint renders infection there specially liable to complications. Damage to this joint is also particularly crippling to the patient. Bone infection adversely affects the prognosis. The significance of delay in treatment was emphasized by Samilson, Bessani and Watkins (1958) who, in their patients, found 77 per cent of the complications in those who had had seven or more days' delay in treatment.

Before the introduction of antibiotics the mortality from acute infective arthritis was about 10 per cent. Of the survivors a useful range of movement was retained in from 36 to 77 per cent (Blaisdell and Harman, 1942; Heberling, 1941; Inge and Liebolt, 1935). Since the arrival of the antibiotics death from this disease has become exceptional. Those patients who would previously have died now survive, although perhaps with a severely damaged joint. The reported success rate of treatment is now 70–89 per cent (Watkins, Samilson and Winters, 1956; Altmeier and Largen, 1952).

Of 23 recent cases reviewed by the writer, full recovery occurred in 20 (87 per cent). Two of the three poor results were in the two patients in whom treatment was not started until after two weeks from the onset of the disease. If treatment is started early and adequate measures are taken to remove the inflammatory exudate, it should now be possible, with use of the correct antibiotic, to ensure full recovery in nearly every case. Unfortunately, delay in diagnosis is still common, particularly in infants and the elderly, and this prevents us obtaining full benefit from these drugs.

COMPLICATIONS

Ankylosis

Severe destruction of the articular cartilage causes permanent loss of movement. When this appears probable, special care must be taken to splint the joint so that ankylosis occurs in the best functional position. Spontaneous bony fusion is not as common as fibrous ankylosis. Arthrodesis is indicated when fibrous ankylosis

Penicillin (25,000 units) injected into a joint cavity will persist at bacteriostatic level for up to two days (McAdam and his colleagues, 1945). Streptomycin persists in effective concentration in the joint for considerably longer (Jones, 1950). The tetracyclines in general are too irritant for local instillation into joints, except in very low concentration. Chloramphenicol succinate may be used but there is, as yet, no information on the reliability of breakdown of this compound into the active antibiotic in joints. Erythromycin, neomycin, Sigmamycin and polymyxin-B sulphate are all theoretically suitable for injection into joints but few published reports are yet available (Edlen, 1959).

The failure of certain antibiotics to appear in the effusion, or their unsuitability for local instillation, is not as serious as may at first appear, because the active site of the disease is in the synovial membrane, which the antibiotics reach without difficulty. The choice of antibiotics must be governed, whenever possible, by a full bacteriological diagnosis and the chosen drug then given in full dosage. During the first 24–48 hours this information is not usually available, and in the instances where the effusion proves sterile knowledge of the causative organism and its sensitivities may never be obtained. On such occasions empirical treatment with a combination of penicillin and streptomycin is justified.

Systemic antibiotic therapy is supplemented, when possible, by local instillation. After each aspiration of the infected joint a solution of antibiotic is injected through the aspirating needle before this is withdrawn. Antibiotic treatment is continued until all evidence of local inflammation has subsided.

When the infection is overwhelming and life endangered, particularly in children, antibiotic therapy is supplemented by careful supportive measures. The correction of anaemia and dehydration by the transfusion of blood and other fluids is most important.

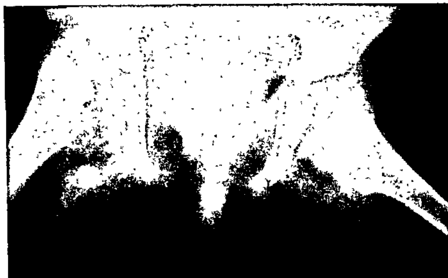
Aspiration and drainage

The removal of the purulent exudate is an important part of the treatment of any localized infection, in a joint or elsewhere. Drainage by incision and the insertion of a rubber tube is, however, to be avoided if possible in the case of joints. Not only does it introduce a risk of secondary infection but the scarring from the drainage track permanently interferes with the free gliding of the periarticular structures one upon the other. In most circumstances adequate removal of the effusion can be achieved by repeated joint aspiration. At the initial diagnostic aspiration, as much fluid as possible should be removed. Aspiration is repeated when the effusion reappears, often 24–48 hours later: it is repeated subsequently as necessary. Aspiration may be stopped when the fluid obtained is no longer cloudy.

Treatment by repeated aspiration is usually entirely satisfactory in superficial joints such as the knee. Drainage by incision is required only in late cases when the joint contains frank pus, or if there is persistent toxaemia. The joint should then be opened by a medial or lateral parapatellar incision and the patient nursed prone to facilitate drainage.

In the hip, drainage by repeated aspiration is more difficult. Complete removal of the effusion is less certain. The amount of fluid in the joint cannot be assessed clinically and hence it is difficult to decide the need for further aspiration. In infants

femoral epiphysis may be absent, the cartilaginous condyle is visible and palpable, and secondary genu valgum or genu varum is not as severe as the bony damage would suggest likely (*see* Fig. 2). In Siffert's case the bony architecture was restored to normal by the time the child was eight years old.



(*a*)



(*b*)

Fig. 5.—(*a*) Pathological dislocation of the hip after suppurative arthritis. The arthrogram (*b*) confirms destruction of the head and part of the neck of the femur. (*Case of Mr. G. C. Lloyd-Roberts.*)

occurs in bad position, or is associated with pain. Bony ankylosis in bad position may be corrected by osteotomy. The risk of a flare of infection is reduced from 34 per cent to 7·6 per cent if the osteotomy is performed at a distance from the original disease (Steindler, 1951). Ankylosis is rare in infancy.

Chronic suppurative arthritis

Chronic suppuration with sinus formation is treated by wide drainage and the removal of sequestrated bone and cartilage fragments. In the fingers amputation may be avoided by a combination of curettage, splinting and antibiotics (Riddell, 1950). Girdlestone's operation (Girdlestone, 1943) for widely draining the hip is applicable to certain cases of chronic suppurative arthritis when more conservative measures have failed.

Dislocation

In subluxation of the hip caused by the mechanical pressure of the effusion, drainage alone will often be sufficient to effect reduction. If there is doubt about the shape of the acetabulum a period of treatment in abduction follows. More often the dislocation is not diagnosed until long after the arthritis has settled. Knowledge of the pathology may then be obtained by an arthrogram (Fig. 5) or by direct exploration of the joint. If the femoral head has not been destroyed reduction is obtained by gradual abduction or by open operation.

Nicholson (1949) found that seven of his ten patients with pathological dislocation of the hip had suffered absorption of the femoral head. In three of these the use of a weight-relieving caliper until the age of 14 years resulted in a shortening of only 1¼–1½ inches. Bryson (1948) has reviewed the alternative methods of treating this condition. Some improvement of stability may be obtained by abduction osteotomy, but the shortening remains and may continue to increase. Leveuf's arthroplasty prevents further shortening and preserves stability and movement. The upper end of the abducted femur is placed in the acetabulum and the great trochanter moved lower down the shaft. At a second stage an adduction osteotomy brings the limb to the normal position. Arthroplasty has also been attempted by the insertion of a fibular graft in place of the femoral head and neck and by a modified "shelf" procedure, but the results are uncertain.

Arthrodesis of the hip is the most reliable solution but cannot be applied until the child is aged 12–13 years.

Dislocation as a sequel of infective arthritis has also been seen in the shoulder and elbow.

Epiphyseal damage

Sequestration of the femoral head epiphysis occurs in severe infections and leads to chronic suppuration from sinuses until the dead bone is removed surgically. Under antibiotic therapy radiographic evidence of necrosis is sometimes seen without sequestration. Revascularization is then possible.

The apparent disappearance in infants of part or all of an epiphysis has already been mentioned. Lloyd-Roberts (personal communication) has confirmed Siffert's (1957) finding that full recovery may occur. Although, for example, half the lower

Makin, M., Alkalaj, I., and Rozansky, R. (1957). "Monoarticular Brucellar Arthritis". *J. Bone Jt Surg.*, **39A**, 1183.
Miller, J. M., and Engle, R. L. (1951). "Metastatic Suppurative Arthritis with Subcutaneous Emphysema Caused by *Escherichia Coli*". *Amer. J. Med.*, **10**, 241.
Mills, L. C., Boylston, B. F., Green, J. A., and Moyer, J. H. (1957). "Septic Arthritis as a Complication of Orally Given Steroid Therapy". *J. Amer. med. Ass.*, **164**, 1310.
Nicholson, J. T. (1949). "Pyogenic Arthritis with Pathologic Dislocation of the Hip in Infants". *J. Amer. med. Ass.*, **141**, 826.
Phemister, D. B. (1924). "The Effect of Pressure on Articular Surfaces in Pyogenic and Tuberculous Arthritides and its Bearing on Treatment". *Ann. Surg.*, **80**, 481.
Riddell, A. G. (1950). "The Treatment of Suppurative Arthritis of the Interphalangeal and Metacarpophalangeal Joints". *Brit. J. Surg.*, **37**, 317.
Reiter, H. (1916). "Ueber eine bisher unerkannte Spirochateninfektion". *Dtsch. med. Wschr.*, **42**, 1535.
Samilson, R. L., Bessani, F. A., and Watkins, M. B. (1958). "Acute Suppurative Arthritis in Infants and Children". *Pediatrics*, **21**, 798.
Siffert, R. S. (1957). "The Effect of Juxta-Epiphyseal Pyogenic Infection on Epiphyseal Growth". *Clin. Orthop.*, **10**, 131.
Smith, A. de F. (1951). "Treatment of Suppurative Arthritis of the Hip by Antibiotics". *Bull. Hosp. Jt Dis.*, **12**, 459.
Steindler, A. (1951). "Pyogenic Arthritis". *Bull. N.Y. Acad. Med.*, **27**, 101.
Sutliff, W. D., Shepard, R., and Dunham, W. B. (1953). "Acute Leptospira Pomona Arthritis and Myocarditis". *Ann. intern. Med.*, **39**, 134.
Watkins, M. B., Samilson, R. L., and Winters, D. M. (1956). "Acute Suppurative Arthritis". *J. Bone Jt Surg.*, **38A**, 1313.

SELECTED ABSTRACTS

Traction lesions of the brachial plexus

Prognosis

BONNEY (1959) gives an account of 29 patients with complete supraclavicular traction lesions of the brachial plexus. In most cases the patients were males, aged 16–25 years, with paresis of the right upper limb due to injuries sustained while riding a motorcycle. Usually the clinical evidence was supplemented by tests of the cutaneous reflexes and of the electrical excitability of the muscles. When funicular biopsy revealed a fairly normal neural architecture and many myelinated fibres, the findings were regarded as an indication that the roots had been avulsed from the spinal cord. Hence a poor prognosis was attached to these findings. No useful recovery was observed either in the intrinsic muscles of the hand or in the extensor muscles of the wrist and fingers. The extent of the damage was invariably too great to warrant resection and repair, but in 15 cases the plexus was explored in order to determine the prognosis. There were no fatalities and no complications, apart from a case of pulmonary collapse due to accidental opening of the pleura. Study of a series of 19 patients revealed useful recovery of power in the trapezius, rhomboids and serratus anterior muscles. Twelve patients showed recovery of the pectoralis major to at least grade 3 in the system devised by the Nerve Injuries Committee of the Medical Research Council. Relatively few patients showed useful recovery of the lateral rotators of the shoulder, the deltoid, biceps and triceps, or the flexors of the wrist and fingers. Sensory recovery was poor, but nutritional defects were not pronounced. Despite their disabilities, 18 patients returned to work. Bonney recommends an exploratory operation 6–8 weeks after the injury if it is considered that the patient is suffering from post-ganglionic lesions of the nerves. Whereas any tearing apart of the plexus can be detected at operation, axon-reflex tests may be of assistance in the diagnosis of intradural preganglionic damage. If the nerves are in continuity conservative treatment should be employed for at least two years. Useful function is not likely to be regained if there are preganglionic lesions in two or more nerves. In these circumstances it may be justifiable to amputate.

SUMMARY

The potential extent of damage to the articular cartilage in acute infective arthritis is determined mainly by the biological activity of the infecting organism.

Diagnosis of the disease in infants and the elderly is often difficult.

Treatment has become much more hopeful with chemotherapy and the use of antibiotics, but these drugs should not be relied upon alone. They must be supplemented by aspiration or, occasionally, by drainage down to, but rarely into, the joint. Joint movements are not started until the infection has been overcome.

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REFERENCES

Altmeier, W. A., and Largen, T. (1952). "Antibiotic and Chemotherapeutic Agents in Infections of the Skeletal System". *J. Amer. med. Ass.*, **150**, 1462.

Applebaum, E., Kohn, J., Steinmann, R. E., and Shearn, M. A. (1952). "Mumps Arthritis". *Arch. intern. Med.*, **90**, 217.

Blaisdell, J., and Harman, P. H. (1942). "Suppurative Joint Disease and its Relation to Pyogenic Osteomyelitis". *Surg. Gynec. Obstet.*, **74**, 796.

Blanche, D. W. (1952). "Osteomyelitis in Infants". *J. Bone Jt Surg.*, **34A**, 71.

Blatchford, R. D. (1953). "Suppurative Arthritis in the Aged". *Lancet*, **1**, 26.

Bryson, A. F. (1948). "Treatment of Pathological Dislocation of the Hip Joint after Suppurative Arthritis in Infants". *J. Bone Jt Surg.*, **30B**, 449.

Collins, D. H. (1949). *The Pathology of Articular and Spinal Diseases.* London; Arnold.

Edlen, A. (1959). "Intra-articular Sigmamycin Treatment of Septic Gonitis". *Svenska Läkartidn*, **56**, 1054.

Florey, H. W., Chain, E., Heatley, N. G., Jennings, M. A., Sanders, A. G., Abraham, E. P., and Florey, M. E. (1949). *Antibiotics.* London; Oxford University Press.

Ford, D. K. (1953). "Natural History of Arthritis Following Venereal Urethritis". *Ann. Rheum. Dis.*, **12**, 177.

Girdlestone, G. R. (1943). "Acute Pyogenic Arthritis of the Hip". *Lancet*, **1**, 419.

Harkness, A. H. (1949). "Reiter's Disease". *Brit. J. vener. Dis.*, **25**, 185.

Heberling, J. A. (1941). "A Review of Two Hundred and One Cases of Suppurative Arthritis". *J. Bone Jt Surg.*, **23**, 917.

Heymann, S., Kessel, I., Jackson, H., Javett, S. N., and Braudo, J. L. (1953). "Septic Arthritis and Osteomyelitis in Infancy". *J. Pediat.*, **42**, 561.

Hutter, C. G. (1948). "New Concepts of Osteomyelitis in the Newborn Infant". *J. Pediat.*, **32**, 522.

Inge, G. A., and Liebolt, F. L. (1935). "The Treatment of Acute Suppurative Arthritis". *Surg. Gynec. Obstet.*, **60**, 86.

Jocson, C. T. (1955). "The Diffusion of Antibiotics through the Synovial Membrane". *J. Bone Jt Surg.*, **37A**, 107.

Jones, B. (1950). *J. Bone Jt Surg.*, **32B**, 437.

Lack, C. H. (1957). "Staphylococcal Antibody in Osteomyelitis and Suppurative Arthritis". *Proc. R. Soc. Med.*, **50**, 625.

— (1959). "Chondrolysis in Arthritis". *J. Bone Jt Surg.*, **41B**, 384.

— and Rogers, H. J. (1958). "Action of Plasmin on Cartilage". *Nature, Lond.*, **182**, 948.

Linsell, W. D., and Fletcher, A. P. (1950). "Laboratory and Clinical Experience with Terramycin Hydrochloride". *Brit. med. J.*, **2**, 1190.

McAdam, I. W. J., Duguid, J. P., Challinor, S. W., and McCall, A. (1945). "Penicillin Treatment of Serous Cavity Infections". *Lancet*, **2**, 843.

tensor fasciae latae, a trough, deep enough to accommodate the transposed iliopsoas, is cut in the wing of the ilium including the base of the anterior superior spine. With the thigh fully abducted and slightly rotated medially, a site is selected for the insertion, under tension, of the lesser trochanter and the attached iliopsoas into the femoral shaft. A window is cut in the femur and the lesser trochanter firmly anchored. The muscles surrounding the iliopsoas are sutured to it. The anterior superior spine is fixed to the iliac crest; the gluteus medius and tensor sutured to the abdominal muscles. A hip spica is applied in a position of medial rotation, slight flexion and full abduction. It is removed at six weeks and non-weight-bearing exercises instituted. After a few days, the patient is allowed up on non-weight-bearing crutches until good abduction is established. Weight bearing with crutches is continued for six months to diminish lurching which may, however, persist in a lesser degree. The range of abduction obtained is sometimes remarkable and patients with poor or fair results after six months often improve considerably in the following years. Muscle transfer should be effective not only in poliomyelitis but in such conditions as arthroplasty with muscular atrophy, congenital hip dislocation, spastic paralysis and myelomeningocele.

Congenital posterior angulation of the tibia with talipes calcaneus

Heyman and his colleagues (1959) discussed congenital posterior angulation of the tibia with talipes calcaneus. In 1949 they described three such cases, suggesting that the deformity was a clinical entity distinct from congenital bowing of the tibia with anterior convexity. The characteristics of the condition are: (1) posterior angulation or backward and medial bowing at the junction of the middle and lower thirds of the tibial diaphysis, with similar bowing of the fibula; (2) severe talipes calcaneus; (3) tightness of the anterior leg muscles and weakness of the triceps surae; (4) a dimple over the angulation; (5) shortness of the leg, with undeveloped muscles; (6) normal bone structure apart from cortical thickening on the concave side; (7) no appreciable impairment of the tibial epiphyses; (8) no unusual tendency to fracture; (9) good prognosis with conservative treatment. This paper concerns the three cases mentioned and eight additional cases. All patients, whose ages ranged from 4 to 18 years, were under observation from infancy; all received conservative treatment. Therapy after birth is confined to massage and stretching of the soft tissues holding the foot in calcaneus; or, in some cases, a removable plaster splint over the anterior aspect of the leg and dorsum of the foot applied with the foot in plantar flexion. From about six months a brace is worn during the day until the tibial bowing is well corrected, the calcaneus deformity eliminated and the triceps surae strengthened. Later, a free joint at the knee is added to the brace which is worn from one to five years. Angulation and calcaneus deformity, unilateral in every case, were completely corrected; the bone density gradually decreased and disappeared. No appreciable radiological abnormality appeared at the epiphyses; shortening only ranged from ½ inch to 2 inches. Epiphyseodesis was performed in two patients, one of the age of 8 years, the other at 11 years. In the first, shortening was corrected by an inch; in the second, by only ¼ inch. A third patient underwent curettage, drilling and insertion of screws at 2½ years with no appreciable benefit. The authors submit that, when the amount of shortening indicates operation, epiphyseodesis of the upper tibial and fibular epiphyses should be performed between the ages of 8 and 10 years. Attempts to stimulate growth by the juxta-epiphyseal introduction of metals are deprecated. In spite of good results from osteotomy conservative treatment is indicated.

Forefoot reconstruction

Fowler (1959) described a method of forefoot reconstruction designed for severe claw toe deformity. In this condition, the toes are drawn on to the dorsum of the foot and the metatarsal heads are prominent in the sole. In 12 of 20 patients, irreversible clawing was associated with rheumatoid arthritis; in the remainder it was associated with hallux valgus or pes cavus. At operation a tourniquet is applied and a dorsal transverse incision is made just proximal to the webs of the toes. After exposing the metatarso-phalangeal joints, the proximal halves of the proximal phalanges are removed. The alignment of the

Dupuytren's contracture

Luck (*1959*) reviewed Dupuytren's contracture, presenting a therapy based upon a new concept of the pathogenesis. The initial manifestation is usually one or more nodules in the ulnar half of the palm or the volar aspect of the proximal half of one or more fingers. With involution, the nodules flatten and contract, and the associated proximal cord enlarges. Contractures are here classified as grades 1, 2 and 3: between 5 and 30 degrees; between 31 and 60 degrees; between 61 and 90 degrees plus. Trauma, formerly considered causative, is now thought to be only an aggravating factor. Heredity, the most definite of all aetiological factors, was evident in 23·4 per cent of 104 cases. The fascial fibrogenic nodule, liable to recur, suggests neoplasm, while its fibromatous appearance during the proliferative stage suggests fascial dysplasia. Although the aetiology is elusive, the pathogenesis is becoming clearer. The essential lesion is a focus of proliferating fibroblasts, usually in the palmer or plantar fascia, creating a palpable nodule, in the involution of which the fibrous cords are intimately related. The three stages of pathogenesis are proliferative, involutional and residual. In the first stage, the nodule resembles a fibroma; solitary or multiple, it is resilient at first. Originating in the palmar fascia, it expands towards the surface, replacing subcutaneous adipose tissue and even deep skin layers. Thus, with a deep attachment to the palmar aponeurosis and a superficial attachment to the skin, its contraction during involution produces a reactive fibrous cord and the flexion contractures of palm and fingers. Contractures take place only within the nodule, the fascial cords representing functional hypertrophy of a fascial band. The only contractures produced by involvement of the palmar aponeurosis are those of the metacarpo-phalangeal joints. The rate of contracture varies from months to years, but eventual contracture is inevitable. In a hand with nodules at stages 1 and 2 therefore, the site and degree of potential contracture can be estimated. With complete involution, the nodule disappears and is replaced by skin drawn into folds and fused with underlying fascia. The cords may be short, existing only in the palm. Treatment, if indicated, is surgical. Non-operative therapy should be limited to cases in which the disease is active and the nodules in the proliferative or early involutional stage. Hydrocortisone injection is disappointing and its use, together with radiotherapy or ultrasonic therapy, should be confined to selected cases. Surgery comprises excision of the nodule, the essential lesion. Subcutaneous fasciotomy of the fibrous cords is indicated in cases of palmar involvement proximal to the webs of the fingers and distal to the apex of the palmar fascia. It is contra-indicated in fingers and thumb and is unnecessary in the proliferative stage. Used alone and routinely, regardless of the stage of the disease, fasciotomy is followed by recurrence. Only that portion of the palm and fingers showing nodules should be the site of open surgery. The operative technique of fasciotomy is described. Complications in this series, few and not serious, included reflex sympathetic dystrophy in three patients. Hypalgesia occurred in eight cases from operative injury to the digital nerve. Contractures recurred in 31 hands; in 19, new nodules appeared in other fingers or in the palmar area away from the surgical site. In the entire group, comprising 206 hands, the results were good in 164, fair in 29, poor in 13.

Iliopsoas transfer for hip instability

A follow-up study

Mustard (1959) presented a follow-up study of iliopsoas transfer for hip instability in 50 patients. Paralysis of the hip abductors is seldom isolated. It is usually accompanied by weakness of the gluteus maximus muscle which, however, does not contra-indicate operation. An incision is made just lateral to the iliac crest and carried anteriorly for about three inches before curving posteriorly to divide the tensor fasciae latae in the thigh. A subperiosteal incision along and over the crest exposes the iliacus. Dissection reveals the anterior superior spine, which is severed. The nerves to the sartorius and rectus femoris muscles are identified. Retraction of the femoral nerve and vessels and of sartorius exposes the lesser trochanter which is divided. It is delivered into the wound with the psoas and iliacus, the iliacus fibres having been shaved off the femur. After division of the

extension across it to the epiphysis. Some cysts may continue to extend after skeletal growth stops; others cease to grow before involving any vital structures. If they are in fact haemangiomas, fibrosis and thrombosis may be expected. In a small cyst this may lead to complete resolution and recalcification; in a larger one, some residual deformity is inevitable. Two large cysts found at necropsy in elderly women and thought to be aneurysmal bone cysts, had fibrous walls with calcified plaques surrounding an endothelial-lined cavity containing thrombus. The whole arose from bone near a cartilaginous growth plate. In the growing child, the cyst wall is probably infiltrating the epiphyseal plate when diagnosis is made; local treatment therefore invites recurrence. The ideal procedure is excision of the cyst and the related epiphysis, when this involves no loss of function. If this is not feasible, radiotherapy in small doses is indicated. In adults accessible cysts may be curetted or excised locally. Radiotherapy is only indicated when an inaccessible tumour is pressing on vital structures or increasing in size. The aetiology is still uncertain, although the appearances of the lesion suggest haemangioma.

REFERENCES

Bonney, G. (1959). *J. Bone Jt Surg.*, **41B**, 4.
Fowler, A. W. (1959). *J. Bone Jt Surg.*, **41B**, 507.
Godfrey, L. W., and Gresham, G. A. (1959). *Proc. R. Soc. Med.*, **52**, 900.
Heyman, C. H., Herndon, C. H., and Heiple, K. G. (1959). *J. Bone Jt Surg.*, **41A**, 476.
Law, W. A. (1959). *J. Bone Jt Surg.*, **41B**, 270.
Luck, J. V. (1959). *J. Bone Jt Surg.*, **41A**, 635.
Mustard, W. T. (1959). *J. Bone Jt Surg.*, **41B**, 289.

metatarsal heads can now be determined; their undersurfaces are trimmed to form an even weight-bearing area. The condylar projections are removed but, in order to make the metatarsals level, it may be necessary in severe cases to excise the whole of the metatarsal heads. If the sesamoids are adherent and do not retract, they also must be excised. The skin alone is sutured, when the toes return to their deformed position. To correct this, an ellipse of skin is removed from the plantar surface behind the metatarsal heads. This must be adequate to accommodate the metatarsal pad when it is replaced. A pressure dressing is applied. Sutures are removed after 2–3 weeks and the toes aligned in a plaster toecap which is worn for four weeks. After removal, an insole with a metatarsal bar is worn in a low-heeled shoe. The follow-up period varies from 1 to 4½ years. Relief and improved activity resulted in every case. Small plantar callosities, usually painless, occurred after six months in seven patients who had not worn metatarsal supports. This operation is a suggested alternative to amputation of the toes and has two advantages: the metatarsal weight-bearing pad is replaced and the cosmetic result is better.

Lumbar spinal osteotomy

LAW (1959) described lumbar spinal osteotomy in just over 100 patients. All were in early adult or middle age; only six were women. With two exceptions, all suffered from ankylosing or rheumatoid spondylitis and presented with a severe rigid kyphosis, mainly cervico-thoracic. The object of operation generally was to provide a compensatory lumbar lordosis. The indications, therefore, were to enable the patients to become erect; to improve respiration by lifting the thoracic cage off the diaphragm and to improve gastro-intestinal function. Operation followed the Smith-Petersen method. Local anaesthesia with adrenaline and general anaesthesia with intratracheal intubation were employed; more recently, fluothane low-pressure anaesthesia has proved excellent. The operation is usually performed at the level of the second or third lumbar vertebra. Through the midline lumbar approach, the muscles are stripped as far as the articular processes and the remains of the intervertebral joints. Part of the spinous process at the lower limit of the intended osteotomy is removed as are the ligamenta flava and the spinous ligaments. Osteotomies are then made across the line of the articular processes at an angle of 45 degrees to the frontal plane from a point just clear of the thecal margin; the completed osteotomy enters the intervertebral foramen above. A certain amount of instability is corrected by hinging the part of the spine above on that below, when the anterior longitudinal ligament is heard to rupture. A wire suture is inserted between the spinous processes, and the surrounding surfaces are prepared for grafting by raising osseous flaps and inserting bone chips which were obtained earlier. Fusion occurs early and consolidation within three months, although longer protection is required. The patient is immobilized in a plaster jacket for six weeks, when the sutures are removed and an ambulatory jacket substituted. The correction achieved at a single osteotomy is usually 25–45 degrees. Eight patients died from post-operative complications. Non-fatal complications included spinal cord irritation, nerve root damage, high intestinal obstruction and ileus. Recurrence of deformity warranting further correction appeared in three cases. In 10 years, however, the loss of correction after operation has been very satisfactory.

Aneurysmal bone cyst

Natural history

GODFREY and GRESHAM (1959) reviewed the natural history of aneurysmal bone cyst, a bone lesion containing spaces filled with blood in continuity with the general circulation. Increasing rapidly in size, it may expand the bone to an extreme degree. Although resembling osteoclastoma in its clinical and radiological appearances, it frequently begins in childhood when osteoclastoma is rare. It is probably a form of haemangioma. Five cases with their histological findings are described. The cyst begins as a proliferation of vascular tissue in the bone adjacent to a cartilaginous growth plate. It grows by active invasion along the blood vessels with early involvement of the epiphyseal plate and

of disability, it is quite incorrect to regard each as a separate and distinct entity which has no relationship to the other forms of the disease. Many cases, originally mild, may progress either slowly or rapidly into the more severe categories (Lewis, and Pickering 1934) and the suggestion that this does not occur can be shown as inaccurate if any large series is analysed, and arises mainly from lack of knowledge of the processes which initiate the disease or give rise to its progression.

The author is of the belief that in the absence of a local precipitating cause or a generalized systemic disease, all forms of Raynaud's phenomenon are related and have an underlying common vascular abnormality, on which may be superimposed additional secondary features which modify the initial presentation, the character of the presenting vascular phenomena and their rate of progression. For this reason the author prefers to use the term primary Raynaud's disease to describe all cases who fulfil the criteria of the primary disease, and the only subdivision used is into mild, moderately severe and severe grades.

Although it is realized that the disease is not entirely limited to the female sex and that in the majority of patients abnormal vascular reactions are present in all four extremities, the clinical presentation is so frequently in the upper extremities that the observations detailed have been confined to females and the blood flow studies limited to the upper limb.

AETIOLOGY

In considering the aetiological factors of importance in Raynaud's disease, it is well recognized that the condition is predominantly one of females in whom there is frequently an inherited predisposition and in whom symptoms commonly arise at an early age, either during childhood or shortly after puberty.

Apart from the sex linkage and the influence of heredity, it is not always appreciated that the disease may either be initiated or its severity increased by events in the patients' lives which occur with sufficient regularity for them to be considered as acquired aetiological factors. The existence of these was originally suggested by Allen and Brown (1932) when, in an analysis of 137 patients they stated: "In a considerable number of cases, the disease appears to be initiated by an operation, childbirth, infection or the death or illness of a loved one". Their observations, however, gave no exact information as to the incidence of each factor and there seems to have been no subsequent series in which their suggestions have been critically evaluated.

In analysing 62 cases referred for surgical treatment during a nine-year period, the various aetiological factors have been carefully assessed by questioning not only the patients themselves but also their relatives.

Hereditary factors

In 54 of the 62 cases referred for surgical treatment an accurate family history was available and in 35 of these (65 per cent) attacks of digital pallor were present in one or both parents. In 28 of the cases attacks had occurred in the mother, in 7 in the father, and in 3 in both parents. In 31 of these cases symptoms of mild Raynaud's phenomenon occurred either during childhood or the early teens

PRIMARY RAYNAUD'S DISEASE: OBSERVATIONS ON ITS AETIOLOGY AND TREATMENT

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INTRODUCTION

The aetiology and treatment of Raynaud's disease have been of interest to investigators and clinicians ever since Raynaud's original classification in 1862. Whereas now it is generally accepted that the vascular phenomena Raynaud described are more accurately grouped into primary and secondary forms, there is still no general agreement either on the nomenclature of the primary disease or the nature of the underlying vascular abnormality.

These two controversial aspects of the disease are in many ways related, as the abnormal vascular reactions are incompletely understood and little is known about the processes which initiate either the mild or the severe forms of the disease. Whereas some authorities use synonymously such terms as idiopathic Raynaud's disease, primary Raynaud's phenomenon, and hereditary cold fingers, others prefer to subdivide patients into separate and unrelated groups, according to the severity of the disease and its mode of onset or progression.

Discussion on the cause has centred mainly around the two theories of Raynaud and Lewis. Whereas Raynaud (1874) considered the disease to be a neurosis characterized by overaction of the vasomotor nervous system, Lewis (1929) concluded that there existed a "local fault" which rendered vessels of the order of the digital arteries hypersensitive to relatively low temperatures. He considered that the sympathetic nervous system was normal and although as the result of subsequent studies (1938) he later stated that in cases with digital necrosis the local fault could be regarded as structural disease of the vessel wall, its nature in the milder forms of the disease was not defined and has remained unknown.

In any investigation of the vascular abnormality in Raynaud's disease, it is essential to realize that the syndrome may present in widely differing degrees of severity. In its mildest form the attacks of digital pallor are infrequent, of short duration, occur only following severe cold exposure, and recovery from them is rapid. At this stage the attacks are painless and give rise to no disability. Between this and the stage of multiple digital ulceration, sclerodactyly, prolonged cyanosis and severe pain, there are infinite degrees of severity. Although it is convenient, and from the point of view of investigation necessary, to classify the phenomena into mild, moderate and severe forms according to the clinical signs and the degree

Discussion

It is apparent from these observations that in the majority of patients with Raynaud's disease there is present an inherited predisposition which manifests itself at an early age. The symptoms at this time are, however, usually mild and give rise to no serious disability. This type of phenomenon, often referred to as "hereditary cold fingers", is extremely common in the general population, being present in 27·5 per cent of 122 young men and women reviewed by Lewis and Pickering (1934) and in 31 per cent of 349 nurses and students investigated by the author. Although these figures indicate that mild attacks of Raynaud's phenomenon are extremely common and that only a small percentage of such individuals will eventually progress to a more severe form, it is not accurate to regard this form of the disease as entirely benign or as a separate entity from those cases which present in later life for medical or surgical treatment. In the 62 patients reviewed in whom symptoms were severe enough for them to be considered for an upper limb sympathectomy, 31 (50 per cent) were individuals in whom a mild form of the disease had been present since an early age and in only 12 could an exacerbating cause be discovered for the increase in severity of their symptoms. In the remainder, a steady deterioration in the efficiency of their circulation had taken place over a period of many years, leading eventually to prolonged periods of cyanosis, pain and nutritional lesions.

In analysing factors other than heredity, it is of interest that in 32 cases (52 per cent) the onset of symptoms sufficiently severe for the individual to seek medical advice could be related to a period of physical or mental stress. In 12 of these cases the effect was to exacerbate symptoms previously mild and present for many years without progression, whilst in 20 cases the symptoms were initiated *de novo.* Cases such as these have frequently been reported by other authors and it is perhaps worth recording that case 5 of Raynaud's original series was one in which symptoms appeared for the first time within a month of the death of the patient's mother; this was considered by Hunt (1936) to be the only true case of Raynaud's disease in the entire group. Hunt's own case, moreover, was one in which mental stress due to separation from her husband may well have been a factor, whilst Ross (1958) has reported a further case in which symptoms occurred for the first time following a post partum haemorrhage, and Reichert (1956) has reported cases following severe infections.

The frequency of these features must of necessity draw attention to the possible role of either the hypothalamus or the pituitary gland in the aetiology of the disease. The sex linkage, together with the occurrence of symptoms at times when considerable changes in endocrine activity are taking place, would indicate that from the aetiological point of view it should be regarded as a neuro-endocrine disease in which either the hypothalamic control of the pituitary gland or the pituitary gland itself is primarily involved.

This concept, of necessity vague in outline, is strengthened by the fact that pregnancy, which represents perhaps the only non-pathological state in which there is a generalized increase in hormone output of the pituitary gland, is invariably accompanied by either a considerable decrease in the severity of symptoms or their complete disappearance.

and in only 4 did the attacks of pallor appear for the first time after the age of 20 years.

In 12 of these patients the symptoms were sufficiently severe during childhood for the parents to seek medical advice for the condition, and in all the other cases the disease was mild and did not initially give rise to any serious disability, although the individuals' outdoor activities were frequently restricted by chilblains during winter months.

Acquired factors

Childbirth

In 11 of the 62 patients the disability which made them seek medical treatment arose within a few months of the birth of a child. In 5 cases the symptoms appeared *de novo* and in the remaining 6, attacks of pallor previously mild and without pain were converted into a more serious form of the disease, pain becoming much more severe and the pallid and cyanotic phases of the phenomenon more intense and prolonged.

Menopause

In 9 cases the digital symptoms were related either to a naturally occurring or an artificially induced menopause. In 5 of these, irregularities of menstruation, which culminated within 18 months in a complete menopause, were present at the time when attacks of pallor previously mild became much more intense, whilst in 4 cases symptoms occurred for the first time during the winter months following a hysterectomy for fibroids. In the latter group one of the operations included bilateral and another unilateral oophorectomy.

Mental stress

A period of mental stress appeared to be an important factor in the occurrence of the disease in 8 cases. In 5 of these, symptoms appeared immediately before or after the death of a mother, father or husband whilst in the 3 remaining patients they arose following a period of unhappy married life which led to separation or divorce. In 7 of these 8 cases the symptoms appeared for the first time within a period of 1–4 months of either the death of the relative or the date of separation and in only one case was there any evidence that a pre-existing mild form of the disease had been present.

Infection and operation

There appeared to be evidence that infections or operations were related to the onset of the disease in 4 cases. In 2 of these cases a history of infective hepatitis was followed the ensuing winter by attacks of digital pallor and in one case the attacks appeared for the first time in a patient who the same year had been operated on three times for acute appendicitis, subphrenic abscess and delayed intestinal obstruction. In the remaining case the digital symptoms followed a subtotal thyroidectomy for thyrotoxicosis and in none of the cases was a pre-existing mild form of the disease present.

assessed. As relatively low rates of flow were presumed to be present in Raynaud's disease, the investigations were undertaken using both digital temperature recording and plethysmography of the hands.

As a result of experimental study at different environmental temperatures it was found that satisfactory conditions for assessing the abnormality were provided by: (1) an in-patient resting state of the individual; (2) an environmental air temperature of 20° ± 0·5°C.; (3) a plethysmograph water temperature of 32° ± 0·5°C. Under these conditions the digital temperatures and hand blood flows of four groups of individuals were measured and compared. The four groups analysed were as follows:

Group 1: Normal controls (20) whose fingers and hands were warm and in whom attacks of digital pallor or cyanosis had never occurred.

Group 2: Grade 1 (mild) Raynaud's disease (8); these were individuals who had not sought medical treatment for their digital symptoms and in whom the attacks were mild, painless and caused no disability.

Group 3: Grade 2 (moderate) Raynaud's disease (20); these were patients who had sought medical advice for their digital symptoms. The attacks were painful, gave rise to a disability and the patients had all been referred for an upper limb sympathectomy. Nutritional lesions were absent in this group.

Group 4: Grade 3 (severe) Raynaud's disease (8); this group comprised patients in whom the digital symptons were severe, being frequent in occurrence, prolonged in duration, and associated with severe pain. Nutritional lesions such as digital necrosis, pulp atrophy, paronychial infection or sclerodactyly were present in all patients.

The results of these investigations are shown in Table I. They indicate that under the conditions defined, the hand blood flows of individuals with all grades of Raynaud's disease are 40–60 per cent below normal. In more exact terms there is a relative ischaemia of 2·6, 3·8 and 2·8 millilitres per 100 millilitres hand blood flow per minute in the three grades of the disease. The digital temperatures, moreover, are similarly subnormal, being 6·1°C., 7·1°C. and 6·6°C. below the normal control standard respectively.

TABLE I

RESTING DIGITAL TEMPERATURES AND HAND BLOOD FLOWS
(Comparison with normal controls at a room temperature of 20° ± 0·5°C.)

Group	*Digital temperature of right index finger °C.*	*Hand blood flow ml./100 ml./min.*
Normal controls (20)	29·4	6·3
Group 1, mild (8)	23·3	3·7
Group 2, moderate (20)	22·3	2·5
Group 3, severe (8)	22·8	3·5

These observations confirm and amplify those of Lewis (1929) that in cases of Raynaud's disease a hypersensitivity exists to temperatures as least as high as 30°C. They show, however, that this hypersensitivity is not limited to those cases which by virtue of nutritional lesions could be classified as severe, but is present in all grades of severity (Peacock, 1959a).

THE VASCULAR ABNORMALITY

Methods of investigating the peripheral circulation

The methods used in the investigation of peripheral blood flow through the extremities are usually those of cutaneous temperature measurement and venous occlusion plethysmography, and the work of Cooper and his colleagues (1949) has been of great value in understanding the relative merits and limitations of these procedures. Their investigations have shown that in a stable hand circulation, at low rates of flow, relatively small increases in blood flow are accompanied by appreciable and relatively large rises in digital temperatures. At digital cutaneous temperatures above 34°C., however, considerable increases in blood flow are associated with relatively small increases in the digital temperatures. Moreover, digital temperatures as high as 34°C., can be recorded when the blood flow as measured by plethysmography and calorimetry is only one-third of that which can be obtained under conditions of full vasodilatation. It can be stated, therefore, that digital temperatures as high as 34°C. may well be recorded in individuals whose circulation is, in fact, considerably diminished by organic disease and absolute skin temperatures cannot be considered of value in estimating degrees of organic arterial obstruction unless these are particularly severe. Skin temperature measurement, however, is of value at low rates of blood flow either under stable conditions or if the changes that occur are slow and relatively small. Under such conditions the errors inherent in the recording and calculation of blood flow by plethysmography may well be greater than the minor changes of flow that take place, and in such circumstances skin temperature measurement may be preferable and more accurate. Caution must also be exercised in the interpretation of graphs, compiled either from digital temperature measurement or venous occlusion plethysmography, which are considered to indicate the presence of organic disease of the vessels due to an abnormally slow vasodilatation following indirect heating.

Roth and Sheard (1950) have shown conclusively that the rates of both vasodilatation and constriction are considerably influenced by variations in the metabolic rate at the time of investigation. Their results indicated that whereas only 25 minutes' exposure to a warm room temperature was necessary to induce a skin temperature of 33°C. in the toes of individuals with high metabolic rates, 180 minutes of exposure was necessary for the same temperature to be recorded if the metabolic rate of the individual was low. These conclusions, which are of particular importance in individuals in whom cold sensitivity is present, can also be shown to be applicable to the thermal state of the individual, and a slow rate of vasodilatation found at a time when the individual's body temperature is relatively low can often be replaced by a much more rapid rate of dilatation if the same investigation is performed at a time when the body temperature is closer to that at which relaxation of vasomotor tone takes place.

Investigations to define the degree of relative ischaemia present in Raynaud's disease

In order to define objectively in terms of blood flow the degree of relative ischaemia present in Raynaud's disease, the necessary prerequisites are to establish initially the experimental conditions under which the abnormality can be detected, and at the same time to define normal standards against which its degree can be

could best be assessed by establishing first of all the experimental conditions which would induce the greatest degree of vasodilatation in the hands of individuals with Raynaud's disease and secondly, by defining the rate of blood flow for normal hands under the same conditions.

Three different methods of inducing vasodilatation in the hands of 10 patients with Raynaud's disease were compared using venous occlusion plethysmography. It was established that the greatest degree of vasodilatation was induced by the use of a high plethysmograph temperature of 42° ± 1°C. and indirect heating to an oral temperature of 37°C. (Peacock, 1958).

Using these experimental conditions the hand blood flows of four groups of individuals were measured and compared. The groups were: normal controls (12); mild (Grade 1) Raynaud's disease (8); moderate (Grade 2) Raynaud's disease (13); and severe (Grade 3) Raynaud's disease (9).

The results of these investigations are shown in Table II. They indicate that a hand blood flow of 30 millilitres per 100 millilitres per minute (mean minus 3 standard deviation) represents the minimal capacity of a normal unobstructed hand to dilate under the conditions of vasodilatation described, and this figure consequently can be considered a standard against which comparison can be made. Failure to reach this level of vasodilatation must be presumed to be due most probably to the presence of organic narrowing or occlusion of the vessels in the hand or the digits.

TABLE II

HAND BLOOD FLOWS UNDER CONDITIONS OF VASODILATATION
(Comparison with normal controls)

Group	*Hand blood flow ml./100 ml./min.*
Normal controls (12) .	36·0 S.D. = 2·0
Mild (Grade 1) (8) . .	32·5
Moderate (Grade 2) (13) .	25·2
Severe (Grade 3) (9) .	20·1

Room temperature 20° ± 0 5°C.

If the plethysmograph estimations of hand blood flow are compared with the histological observations of Lewis, it can be seen that they agree with and confirm his conclusions in the mild and severe forms of the disease.

In the cases of moderate severity, however, only 3 of the 13 hands investigated showed a normal capacity to dilate, and in 10 of these (77 per cent) this was subnormal often to quite a severe degree (Peacock, 1958). These findings are of importance because they imply that there is probably present in the majority of such cases a subclinical degree of organic arterial disease which is absent in the mild form of the disease. In addition, they indicate that conclusions reached as to the role of the sympathetic nervous system in this group are not necessarily accurate if the assumption that there is no structural arterial disease present is based purely on clinical grounds. Although Lewis did not specifically investigate the histological features of the arteries in cases of this type, the plethysmograph investigations do confirm his observations, in the more severe group, that a considerable degree of organic disease can be present in the arteries supplying digits in which there is no clinical evidence of its presence. Organic arterial obstruction by itself does not

Structural disease of the arteries in primary Raynaud's disease

The presence or absence of structural disease of the blood vessels of the hand or fingers is of fundamental importance in Raynaud's disease, particularly if the role of the sympathetic nervous system is being selectively assessed. Knowledge of this aspect is in the main derived from the classical, detailed and extremely accurate observations of Lewis (1938) who compared the histological appearances of the arteries of the hands and fingers of six cases of Raynaud's disease with those of arteries taken from 18 individuals in whom attacks of pallor or cyanosis had been absent during life. The symptoms in three of the cases were mild with no pain, progression or disability and the patients were under medical care for other diseases. No evidence of organic disease was found in two of these subjects, whilst in the third, the lumens of the digital arteries were considered to be narrowed by intimal hypertrophy which was no greater in degree than that found in older individuals whose hands were normally warm. Lewis considered that the attacks of pallor or cyanosis in such cases resulted from overaction of the muscle wall as there was no evidence of medial hyperplasia of the arterial wall. In the three other cases the disease was classified as severe (Grade 3), as the symptoms were progressive and nutritional lesions of the digits were present. Although considerable degrees of organic disease were found in the vessels of these cases, the changes were not limited to the arteries of those digits in which scarring or unhealed necroses furnished clinical evidence of its presence, but were also present in arteries supplying fingers in which no such complications had occurred. As a result of these investigations it could be stated that in cases with scarring or necrosis of digits, structural disease of the arteries is invariably found, but lack of these clinical features does not preclude subclinical degrees of organic disease, possibly severe, from being present.

In an attempt to evaluate this possibility, several authors (Allen, 1937; Lynn, Steiner and Van Wyk, 1955) have performed arteriograms of the hand and fingers in patients with Raynaud's disease. Their observations, however, were either inconclusive or could be criticized on the grounds that no adequate series of controls were studied. Arteriography, although of value in isolating segmental blocks, cannot be considered of value in measuring minor changes in calibre as considerable changes can be present at operation in vessels, even major ones, which previous arteriography has shown to be radiologically normal. Moreover, the inevitable occurrence of vasospasm associated with intra-arterial puncture and the injection of contrast media (Wickbom and Bartley, 1955) renders the results difficult to interpret and potentially fallacious.

In view of the histological features reported by Lewis and the finding by the author of relative ischaemia in all grades of Raynaud's disease, it appeared essential before assessing the role of the sympathetic nervous system to establish if possible the degree of organic arterial occlusion present in the three grades of the disease.

It is logically and universally accepted that organic narrowing or occlusion of the arteries supplying an organ or part will result in a diminution of the capacity of that organ or part to undergo vasodilatation. It was considered probable, therefore, that in view of the high rates of flow present in the vessels of the hand and digits under conditions of full vasodilatation, minor as well as major degrees of occlusion

skin of the digits following occlusion. Its severity and the ease with which it could be demonstrated was related to the severity of the patient's symptoms and the ease with which attacks of cyanosis could be induced pre-operatively. In the fourth patient, whose symptoms were mild and in whom no attacks could be induced pre-operatively, no abnormality could be demonstrated following sympathectomy and reactionary hyperaemia after occlusion was normal.

Although Lewis performed a number of additional experiments which indicated that some degree of local cooling of digits was essential for the development of clinical cyanosis, these were complementary to the other two groups of observations, and did not give such direct evidence about the role of the sympathetic nervous system as was provided by the experiments performed on patients in whom the vasomotor control of the digits was presumed to have been removed.

If Lewis's experiments are re-examined, however, certain criticisms must be made in the light of knowledge to which Lewis himself has been a major contributor.

The conclusion reached originally that the vasomotor nervous system was normal (Lewis, 1929) was made as the result of his interpretation of the vascular reactions of digits in which structural arterial disease was almost certainly present. Although it would be accurate to state that in such patients the disease was not the result purely of an abnormality of the sympathetic nervous system, it does not appear possible to analyse selectively under such circumstances the role of the vasomotor nervous system alone. In the second group of patients, moreover, the author has shown that in many such cases there is a subnormal capacity of the hand and digital vessels to undergo vasodilatation. This abnormality, together with the delay in the development of a reactionary hyperaemia, could well be explained by the presence of subclinical degrees of structural arterial disease which are absent in the milder forms of Raynaud's disease.

INVESTIGATIONS OF THE SYMPATHETIC NERVOUS SYSTEM

Plethysmographic studies

Plethysmograph measurements of the hand blood flows in controls under in-patient resting conditions at a fixed environmental temperature have enabled a curve of hand blood flow to be compiled, which can be used as a standard against which the abnormality present in Raynaud's disease can be assessed in terms of relative ischaemia over a wide local temperature range of 17°–42°C. in water (Fig. 6).

If the hand blood flows of cases of primary Raynaud's disease are compared with this normal curve under identical conditions, the vascular abnormality present in the disease becomes apparent. To analyse selectively the role of the sympathetic nervous system in primary Raynaud's disease, it was felt to be essential that both clinically and by blood flow studies the presence of structural disease of the vessels should be excluded. Twenty-two hands of 21 cases of the disease in which these measurements were undertaken were therefore again classified into three grades.

Grade 1: Nutritional lesions of digits absent. Normal capacity of the hands to undergo vasodilatation.

Grade 2: Nutritional lesions of the digits absent. Capacity of the hand to undergo vasodilatation subnormal.

necessarily lead to nutritional changes in digits as it is quite frequent for the severe cases to develop, in the cold winter months, digital necroses which subsequently heal as the environmental temperature becomes warm. There is no evidence to suggest that cold by itself will influence the degree of organic occlusion, and it is probable that its effect is either to induce direct vasoconstriction or to modify the ability of the digital vessels to recover from occlusion, whether this is induced by cold or pressure. Such an effect could be due either to a loss of elasticity of the vessel wall or more probably to a delay in the development of a reactionary hyperaemia which accompanies a diminished pulse pressure and a decreased arterial inflow. Clinically, such cases are characterized by a change over a period of time in the character of their symptoms, the intensity and duration of the pallid and hyperaemic phases of the syndrome being decreased and the cyanotic stage of the attacks prolonged.

It is considered, therefore, that structural disease of the arteries, often subclinical, is present in the majority of patients with Raynaud's disease who present with a painful disability for medical treatment. This factor constitutes a major difference between these individuals and those in whom the disease is mild and without pain.

THE SYMPATHETIC NERVOUS SYSTEM

The role of the sympathetic nervous system is perhaps the most discussed and controversial aspect of primary Raynaud's disease, and it is relevant at this stage to review the two main theories that exist as to the nature of the underlying vascular abnormality.

The evidence on which Raynaud's theory (1874) is based consists mainly of four clinical observations which are circumstantial in character and found in a minority of patients with this disease. They cannot be considered in themselves specific enough to justify any definite conclusion being reached as to the role of the vasomotor nervous system. Although it may well be said that the observations Raynaud reported are sufficient to indicate the possibility that an abnormality is present in the sympathetic nervous system, they do not constitute in themselves sufficient proof that such is in fact present.

The evidence which Lewis (1929, 1938) presented to substantiate his theory followed both scientific and clinical investigations of patients, which must be regarded as classical examples of research in clinical medicine. If his investigations are analysed, however, it is found that his conclusion that the vasomotor nervous system is normal is based mainly on two groups of observations.

The first of these, made in two patients, was that an ulnar nerve block failed (*a*) to prevent an attack of cyanosis being induced by local cold in the anaesthetized digits, and (*b*) to relieve completely an established attack of cyanosis in digits which were maintained at a cold environmental temperature in water.

The second group of observations made subsequently on four patients without nutritional lesions of the digits (Lewis, 1938) was that removal of sympathetic nervous control of the hand and digital vessels by surgical sympathectomy did not in three of the four cases completely abolish the abnormal response of the digital vessels to local cold or occlusion. The residual abnormality consisted essentially of a delay in the rate at which reactionary hyperaemia invaded the vessels of the

skin of the digits following occlusion. Its severity and the ease with which it could be demonstrated was related to the severity of the patient's symptoms and the ease with which attacks of cyanosis could be induced pre-operatively. In the fourth patient, whose symptoms were mild and in whom no attacks could be induced pre-operatively, no abnormality could be demonstrated following sympathectomy and reactionary hyperaemia after occlusion was normal.

Although Lewis performed a number of additional experiments which indicated that some degree of local cooling of digits was essential for the development of clinical cyanosis, these were complementary to the other two groups of observations, and did not give such direct evidence about the role of the sympathetic nervous system as was provided by the experiments performed on patients in whom the vasomotor control of the digits was presumed to have been removed.

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Grade 1: Nutritional lesions of digits absent. Normal capacity of the hands to undergo vasodilatation.

Grade 2: Nutritional lesions of the digits absent. Capacity of the hand to undergo vasodilatation subnormal.

Grade 3: Nutritional lesions of the digits present. Capacity of the hand to undergo vasodilatation subnormal.

Cases in Grade 1 are believed to be patients with Raynaud's disease in whom structural arterial disease is almost certainly absent, whereas cases in Grade 3 are considered to be cases of the disease in which organic arterial disease is undoubtedly present (Lewis, 1938). Grade 2 cases are believed by the author to be those in which there is present a degree of organic arterial disease which is subclinical, but which has not given rise to nutritional lesions and may be at a site in either the palmar or digital vessels which has allowed a diminution in blood flow to occur without inducing peripheral nutritional lesions. The distribution of cases into the three grades were as follows: Grade 1—3 hands; Grade 2—9 hands; and Grade 3—10 hands. It can be seen from these figures that it is uncommon to find that the hands of patients with Raynaud's disease are both clinically without nutritional lesions and also have a normal capacity to undergo vasodilatation.

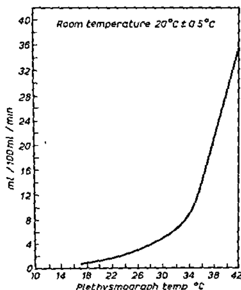


Fig. 6.—Graph showing normal hand blood flows. This can be used as a standard to assess the abnormality present in Raynaud's disease.

If the mean hand blood flows of this group (Grade 1) are compared with those of normal female controls, an abnormality is present which is detectable at a plethysmograph temperature of 34°C. (Fig. 7). At this temperature there is a reduction in hand blood flows relative to that of normal controls of 2·4 millilitres per 100 millilitres per minute which is a percentage deficit of 24. At 32°C. local temperature, the deficit is 2·9 millilitres per 100 millilitres per minute which is a percentage deficit of 47 and at 27°C. the deficit is increased to 70. At a plethysmograph temperature of 22°C. no blood flow was detectable in any of the three hands measured. These figures indicate that in primary Raynaud's disease an abnormality is present at quite a high local hand temperature and that it is increased and potentiated by lowering the local temperature of the hand. This does not imply that the abnormality is purely local in origin, as decreasing the local environmental temperature constitutes both a direct and an indirect cold stimulus, but it does indicate

that local cold is an important factor in maintaining and increasing the degree of relative ischaemia in this disease.

The mean hand blood flows of Grade 3 cases are also of interest as it can be seen that structural arterial disease by itself does not increase the degree of ischaemia present in the lower temperature range (Fig. 8). Its effect, as previously suggested, is probably to modify the vascular reactions of the vessels by decreasing the effective arterial inflow. This, although not necessarily decreasing the final blood flow, which will be mainly conditioned by the effect of local cold itself, will result in a delay in the speed of recovery of such vessels from cold or occlusion, due to a reduction in the rate at which reactionary hyperaemia can develop once the cause of occlusion has been removed.

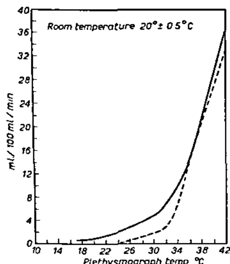


FIG. 7.—Comparison of normal hand blood flows (solid line) with Grade 1 primary Raynaud's disease (broken line). (*By courtesy of the Editor, Clinical Science.*)

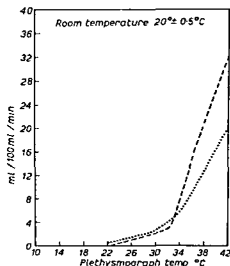


FIG. 8.—Comparison of hand blood flows of Grade 1 (broken line) and Grade 3 (dotted line) primary Raynaud's disease.

The plethysmographic investigations therefore define in terms of hand blood flow the degree of ischaemia present in cases of primary Raynaud's disease relative to normal controls. They also enable the abnormality present in cases without structural arterial disease to be selectively defined and analysed.

The release of vasomotor nervous control of the hands and digits

The release of vasomotor nervous control of the hand and digital vessels can be secured by either indirect body heating, interruption of nerve conduction, adrenergic blocking drugs or surgical sympathectomy. Although the effect of complete sympathetic inhibition has been studied in all three grades of the disease, as the role of the sympathetic nervous system is being selectively analysed, the results in this section are limited only to the investigations performed in Grade 1 patients in whom structural and arterial disease can be presumed to be absent.

Acute and temporary release of vasomotor nervous control

The clinical effect of a brachial plexus and stellate ganglion block was observed, together with its effect on the hand blood flows of three Grade 1 patients with Raynaud's disease over a plethysmograph temperature range of 17°–42°C. The results of these investigations were compared with identical measurements following an intravenous infusion of phenoxybenzamine. This latter drug was given in a dose of 2 milligrams per kilogram body-weight, as preliminary observations had indicated that this concentration was necessary before complete adrenergic blockade was achieved.

Results.—The effect of both these procedures (Table III) was to induce a considerable increase in the hand blood flows of these patients at all plethysmograph temperatures between 17°C. and 42°C. The rate of hand blood flow at a plethysmograph temperature of 17°C. remained high although immersion of the hand was maintained for a period of an hour in each case. The hand and digital blood flows were in fact sufficiently rapid to necessitate continuous cooling of the water in the plethysmograph owing to considerable heat exchange from the dilated peripheral

TABLE III

ACUTE AND TEMPORARY RELEASE OF VASOMOTOR NERVOUS CONTROL

Case no.	*Plethysmograph temperature °C.*						
	17°	22°	27°	32°	34°	36°	42°
1	6·0	12·8	19·9	21·4	25·3	28·4	30·2
2	9·2	21·0	24 0	29 2	32·2	34·3	36·1
3	6·8	15·3	19·7	24·3	26·0	29·2	32·2
	Intravenous phenoxybenzamine 2 mg./kg./B.wt.						
1	8·0	14·2	21·3	28·0	30·1	32·2	38·3
2	11·3	18·2	24·2	29·3	33 0	35·1	37·2
3	9·2	17·3	21·2	27·6	30 0	31·6	34·7

The effect of (1) a brachial plexus and stellate ganglion nerve block, and (2) an intravenous infusion of phenoxybenzamine (2 milligrams per kilogram body-weight) on the hand blood flows. (Ml. per 100 ml. per min room temperature 20 C.)

hand and digital circulation. At no time was it possible to detect any cyanosis or pallor and subsequent immersion of the hands in water at 15°C. was without any detectable effect, the hands and digits remaining pink and the digits warm. On removal of the hands from water at 17°C. the digital temperatures reached 33·8°–35·2°C. within a period of four minutes and it was obvious that the rate of blood flow was extremely rapid in all digits. The effect of the sympathetic nervous interruption on the one hand and complete adrenergic blockade on the other was to render it quite impossible to induce any attack of either digital cyanosis or pallor in any of these patients by local cold. In these patients, therefore, the acute interruption of nervous control of the hand and digital vessels had completely abolished any evidence of peripheral vascular ischaemia and no residual vascular abnormality could be detected.

Chronic release of vasomotor nervous control of the hands and digits by surgical sympathectomy

After a surgical sympathectomy there follows a period of vasodilatation lasting 2–3 days, during which the pattern of hand blood flow is comparable to that induced by acute and temporary sympathetic blockade. This stage of maximum vasodilatation rapidly subsides and by the end of the second week the hand blood flows have fallen to about an eighth of those recorded in the immediate post-sympathectomy period (Barcroft and Walker, 1949). In three cases of Grade I Raynaud's disease the hand blood flows followed this general pattern but it was apparent that in the lower temperature range they never returned to their pre-operative levels. During the ensuing weeks a stable pattern of hand blood flow gradually became established which, from the third month onwards, remained remarkably constant until such a time as vasomotor nervous control of the hand and digital vessels returned. This pattern was measured in three patients with Grade I Raynaud's disease, and, compared with their pre-operative hand blood flows under identical conditions (Table IV, Fig. 9), it was apparent that the effect of the

TABLE IV

Comparison of Hand Blood Flows before and 3–6 Months after an Upper Limb Sympathectomy

Case no.	*Plethysmograph temperatures °C.*													
	Pre-operative							*Post-sympathectomy*						
	17°	22°	27°	32°	34°	36°	42°	17°	22°	27°	32°	34°	36°	42°
1*	0	0	1·8	3 8	6 0	17·1	32·3	·9	1·7	3·7	5·9	9·3	16.7	30·1
2†	0	0	0	1·8	9·5	14·6	33 0	·8	1·6	3·4	6·2	11 6	16·2	31 0
3‡	0	0	1·7	3·2	7·0	14·1	32·3	1·2	2·2	4·0	6·5	9 2	14·4	35·1
Mean	0	0	1·2	2·9	7 5	15·3	32·5	·9	1·8	3·7	6·2	10 0	15·8	32·1

ml. per 100 ml. per min , room. temperature 20° ± 0 5°C.

* Transthoracic excision of inferior cervical and T 1–T.5 ganglia.
† Excision of inferior cervical and T.1, T.2 and T.3 ganglia.
‡ *See* Fig. 9

surgical sympathectomy was mainly confined to the hand blood flows in the plethysmograph temperature range below 36°C., and at the higher plethysmograph temperatures the hand blood flows were essentially unchanged. As sympathetic nervous control of the hand and digital vessels in these patients had been removed, the effect of cold was now purely direct and local. The hand blood flows of all these patients were almost identical and were now in the normal range at all plethysmograph temperatures. The patients themselves stated that they had experienced no further attacks of digital pallor or cyanosis since the operation and on examination their hands appeared entirely normal. Immersion of the hands and digits of these patients in water at 17°C. and later at 15°C. for an hour induced no abnormality in the digits, and subsequent lowering of the room temperature from 20°C. to 10°C. did not give rise to any digital pallor or cyanosis.

It was concluded, therefore, that in these three cases in whom structural disease of the arterial inflow had been almost certainly excluded, both the degree of

ischaemia relative to normal controls and the *presenting vascular phenomena* resulted from an abnormal degree of vasoconstriction, the cause of which was mediated entirely through the *sympathetic nervous system.*

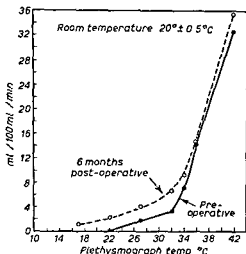


Fig. 9.—Primary Raynaud's disease (Grade 1): *comparison of pre-operative hand blood* flows with those six months after cervico-dorsal sympathectomy

Summary

Although it has been possible to establish the role of the sympathetic nervous system in these three patients in whom the symptoms were of only moderate severity, it has not been possible, using these methods, to analyse selectively its role in the more severe forms of the disease. Comparison of the hand blood flow patterns in the three grades of the disease (Peacock, 1960a) suggests the probability that increasing degrees of organic arterial disease are superimposed upon a primary abnormality of the sympathetic nervous system, but in themselves do not constitute sufficient proof that such is in fact the case.

VASOCONSTRICTOR SUBSTANCES IN RAYNAUD'S DISEASE

In view of the discovery by von Euler (1946) that noradrenaline as well as adrenaline is present in sympathetic nerves, and the demonstration by Peart (1949) and later Mann and West (1950) that noradrenaline is released in high concentrations when adrenergic nerves are stimulated, it was thought possible that an analysis of the concentration of vasoconstrictor substances in peripheral venous blood might be of value in detecting whether an abnormality of the sympathetic nervous system is present in Raynaud's disease. Peripheral venous samples taken from the dorsum of the wrist of nine female patients with Raynaud's disease and six normal controls were analysed by paper chromatography and biological assay.

The samples were linked with simultaneous hand blood flow recordings of the opposite hand and were taken under two different environmental conditions: (1) under warm resting conditions at an environmental temperature of 26° ± 1°C. and (2) during a severe cold stimulus to the abdominal wall.

The hand blood flows were subnormal in all cases of Raynaud's disease under both circumstances. Whereas no evidence of vasoconstrictor substances could be detected in the blood of normal controls, the mean values of both adrenaline and

noradrenaline were abnormally high in patients with Raynaud's disease (Table V, Fig. 10). The adrenaline and noradrenaline blood levels were elevated under warm

TABLE V

HAND BLOOD FLOWS AND THE LEVELS OF VASOCONSTRICTOR AMINES IN PERIPHERAL VENOUS BLOOD
(Comparison with normal controls)

Group	*Hand blood flows ml./100 ml./min.*	
	Warm	*Cold*
Normal controls (6) . .	11·4	3·2
All grades primary Raynaud's disease (9) . . .	4 9	0 7

µg. per 100 ml. blood (estimated in plasma)

Group	*Warm*		*Cold*	
	Adrenaline	*Noradrenaline*	*Adrenaline*	*Noradrenaline*
Normal controls (6) . .	0	0	0	0 (5) 0·2 (1)
All grades primary Raynaud's disease (9) . . .	1·9	1·9	4·2	9 0

(1) Warm resting conditions at environmental temperature of 26° ± 1°C.
(2) During cold constrictor stimulus.

resting conditions in 5 and 7 patients respectively, and following the cold stimulus the blood adrenaline levels were increased in 8 cases and the noradrenaline concentrations in 7 (Peacock, 1959b). The degree of increase in the noradrenaline fraction was found to parallel very closely the clinical severity of the patients' symptoms for whereas there was no increase in 2 cases in which the disease was mild and non-progressive, in 6 other patients in whom the symptoms were more

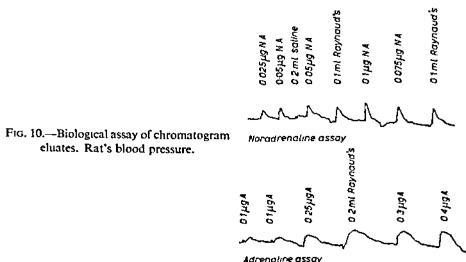


FIG. 10.—Biological assay of chromatogram eluates. Rat's blood pressure.

severe and progression of the disease was occuring, the noradrenaline concentrations were considerably increased, in several to high values.

The vasoconstrictor substances isolated are considered to arise in the main, if not entirely, from the sympathetic nerve endings, as following a surgical sympathectomy the degree of peripheral vasoconstriction that can be induced by an indirect cold stimulus is small and of little practical importance. The cause of these high concentrations is of interest and several mechanisms could be involved. Smith (1952) has shown that both the degree and duration of adrenaline-induced arterial constriction are considerably increased by lowering the temperature of the arterial wall, and considered that this was due to the effect of temperature on the enzymatic systems which inactivate adrenaline. Whelan (1951), moreover, has shown that in hands the degree of vasoconstriction induced by noradrenaline is considerably enhanced by lowering the local temperature of the hand; whereas at 44°C. only a 12 per cent reduction in blood flow occurred in response to a standard dose, at 32°C. the degree of vasoconstriction was increased to 55 per cent. In Raynaud's disease the average digital cutaneous temperature in an environmental temperature of 20°C. is 22·3°C. compared with 29·4°C. in normal individuals (Peacock, 1959a) and it is highly probable that the intraluminal temperature of the digital arteries in patients with Raynaud's disease is considerably lower than in normal controls due to pre-cooling of arterial blood (Bazett, 1949).

A further mechanism possibly involved is the concentration of amine oxidase in the vessel walls. Although the role of amine oxidase in the peripheral inactivation of adrenaline and noradrenaline has not been finally established, it is of interest that its presence could not be detected in the digital arteries of one case of the disease in which it was estimated, whilst in digital arteries removed for non-vascular reasons the concentration was found to be $552\mu l \cdot O_2$ per gramme per hour. Although further estimations of this enzyme are necessary for this to be considered more than a possible hypothesis, it does suggest that an abnormality in this enzyme system might be present.

Summary

It would appear from these investigations that there is present in all patients with Raynaud's disease an abnormality in the peripheral production or metabolism of sympatheticomimetic amines. The results are believed to indicate the presence of an abnormality either in the sympathetic nervous system itself or in the enzymatic systems which inactivate the neurotransmitter substances liberated by it. The significantly lower level of hand blood flow present in the patients investigated is considered to have been partially or wholly induced by an abnormal degree of vasoconstriction mediated through the sympathetic nervous system.

ENDOCRINE AND METABOLIC STUDIES

The aetiological factors associated with the initiation or exacerbation of Raynaud's disease suggested that endocrine abnormalities might be present which could influence either the degree of vasomotor activity or the level of tissue metabolism. As a result the endocrine and metabolic states of 20 patients with Raynaud's

disease were investigated and compared with those of a normal series of female controls.

Results

The results, when analysed as a single group (Table VI), suggested that an endocrine abnormality was present in which a low level of circulating thyroid hormone and an increased thyroid uptake was associated with a low urinary excretion of oestrogens and a relatively normal adrenal secretion. When subdivided according to their aetiological cause, however, this interpretation was found to be fallacious as considerable variations in glandular activity were apparent when individual groups were assessed and compared (Table VI). Although the series divided in

TABLE VI

ENDOCRINE AND METABOLIC STUDIES
(Comparison of means: single group analysis)

Group	^{24}U ^{131}I	*Serum protein bound iodine µg./100 ml.*	*17-ketosteroids mg./24 hrs.*	*Per cent β-ketosteroids*	*17-ketogenic steroids mg./24 hrs.*	*Urinary oestrogens µg./24 hrs.*	*Basal metabolic rate (per cent)*
Normal female controls (20)	40	5·1	9·0	6·2	9·2	24·1	+2
Primary Raynaud's disease (21) . . .	48	3·3	6·7	4·9	8·1	11·3	−5

(Comparison of means: primary Raynaud's disease divided according to aetiological causes*)

Aetiological cause: No. of cases	^{24}U ^{131}I	*Serum protein bound iodine µg./100 ml.*	*17-ketosteroids mg./24 hrs.*	*Per cent β-ketosteroids*	*17-ketogenic steroids mg./24 hrs.*	*Urinary oestrogens µg./24 hrs.*				*Basal metabolic rate (per cent)*
						OH	*2OH*	*3OH*	*Total*	
Hereditary (3)	41	2·8	12·5	13·9	10 0	3·2	2·8	4·6	10 6	0·5
Mental stress (4)	48	4·9	5·3	2·5	6·2	5·3	3 0	3·0	11·3	+8
Post partum (5)	49	3·1	4 0	1·8	6·6	3·5	2 8	2·6	8 9	−12
Menopausal (4)	55	3·1	5·4	2·8	10 0	6·1	4·1	4·1	14·3	− 7
Unknown (4)	49	3 3	6·7	4 3	7·5	5·3	4·2	4 0	13·5	−14

* One case following thyroidectomy not included as a group.

this way represents relatively small groups of patients, it is clear that essential differences in the endocrine patterns of the hereditary and acquired groups of patients preclude their being grouped into any one syndrome that can be regarded as specific for Raynaud's disease.

Hereditary group

In the group of patients in which the disease was related to an inherited predisposition, a low level of circulating thyroid hormone and a normal thyroid uptake are associated with a low urinary excretion of oestrogens and adrenocortical activity in the highest normal range. The metabolic rate is normal.

Acquired aetiological groups

Mental stress

In those patients in whom symptoms followed a period of emotional stress, the circulating thyroid hormone is normal and the thyroid uptake is in the highest normal range. The urinary oestrogen excretion is low and adrenocortical activity is in the lower normal range. The 17-ketosteroids are low and the metabolic rate is in the higher normal range.

Post-partum group

In those patients in whom symptoms appeared *de novo* or were exacerbated following childbirth, the circulating thyroid hormone is low and the thyroid uptake is in the highest normal range. The urinary oestrogen excretion is low and adrenocortical activity is in the lower normal range. The 17-ketosteroids are low and the metabolic rate is at the lowest limit of normal.

Menopausal group

In the menopausal group of patients the circulating thyroid hormone is low and the thyroid uptake above normal. The urinary oestrogen excretion is in the normal range and adrenocortical activity is normal. The 17-ketosteroids are relatively low and the metabolic rate is in the lower normal range.

Unknown factor group

In the patients in whom vascular symptoms occurred without any hereditary or known acquired aetiological factor being present, the circulating thyroid hormone is low and the thyroid uptake is in the highest normal range. The urinary oestrogens are low and adrenocortical activity normal. The 17-ketosteroids are in the lower normal range and the metabolic rate is subnormal.

Discussion

The exact cause of these abnormalities is not clear and although it would be convenient to suggest that the multiplicity of the abnormalities can only be explained as being the result of a pituitary defect the investigations so far do not entirely support this concept. Although Reichert (1956) has claimed that in Raynaud's disease a derangement of the pituitary gland is associated with depletion of the adrenal cortex, in the hereditary group of the disease in which any abnormality specific to the disease might be expected to be present, the adrenal function is in the highest normal range.

The cause of the low level of circulating thyroid hormone and low urinary oestrogens, which are present in four of the five groups is obscure and the relationship of thyroid activity to oestrogen secretion or administration is controversial and incompletely understood (Ciba Symposium, 1957). The diminished oestrogen excretion in the hereditary group of patients would appear to be most probably ovarian in origin as menstrual irregularities are uncommon in these patients and adrenocortical activity is high. In the acquired groups of the disease, however, menstrual irregularities are much more frequent, being present in all three cases in whom symptoms occurred following mental stress, four of the five cases following

childbirth and two of the four patients in whom the aetiological cause was unknown. In these groups it would appear more likely, particularly in view of the relatively lower level of adrenocortical activity, that the oestrogen deficiency was secondary to pituitary dysfunction.

Although these variations indicate that there is no specific endocrine abnormality common to all patients with Raynaud's disease, it would be wrong to suggest that these abnormalities are of no importance in influencing the character of the vascular abnormality in Raynaud's disease or that they are of little value in suggesting possible methods of treatment. The cholinergic activity of oestrogens is well recognized (Lecoq, Chauchard and Mazoué, 1952) and although the author is in agreement with Reynolds and Foster (1939), that in physiological doses oestrogens exert little influence on the total digital or hand blood flow, there is no doubt that they influence capillary flow and decrease cyanosis of capillary origin. The relatively normal level of excretion of the 17-ketogenic steroids indicates that the low level of circulating thyroid hormone in four of the five groups of the disease, and the relatively low level of the 17-ketosteroids in the acquired groups, constitute the only other abnormalities which need be considered.

In investigations discussed under the treatment of Raynaud's disease it was found that both triiodothyronine and testosterone could considerably increase the level of tissue metabolism. Whereas triiodothyronine when given to patients with a relatively normal level of 17-ketosteroid excretion was accompanied by a considerable rise in tissue metabolism and peripheral blood flow, in cases with subnormal levels of ketosteroid excretion it was largely ineffective and testosterone therapy was necessary before the metabolic rate was increased by its use. It is noteworthy that whereas in the hereditary group of the disease and those following mental stress the metabolic rates of the patients are in the normal or upper normal range, in the three other groups in which a relatively low urinary excretion of 17-ketosteroids was associated with a low serum protein bound iodine, the metabolic rates were either in the lower normal range or subnormal. It is thought to be highly probable that in patients with an abnormal degree of vasomotor tone the effect of the diminished excretion of 17-ketosteroids and low serum protein bound iodine is to induce a low level of tissue metabolism and a further decrease in the peripheral blood flow. The result of this is to decrease the ability of such patients to overcome vasoconstriction (Roth and Sheard, 1950). Clinically, the cyanotic phase of the phenomenon is prolonged, the duration of the peripheral ischaemia increased and the patient's disability exacerbated.

TREATMENT

Upper limb sympathectomy

Although many of the cases of primary Raynaud's disease are mild and the degree of disability is not such as to justify operative treatment, sympathectomy has for the last 30 years been regarded as the treatment of choice for the vast majority of patients in whom the attacks are painful or in whom a disability is present which interferes with their normal way of life.

There can be no doubt that a considerable degree of permanent benefit follows surgical sympathectomy in many patients, although the exact degree is controversial

and shows considerable variation when published series are compared. This discrepancy is due not only to considerable differences in clinical classification and selection of patients for operation but also to the varying post-operative periods at which results are assessed and reported. In addition, clinical criteria of what constitutes a good result or a failure must of necessity be a variable which is difficult to evaluate when several series of cases by separate authors are analysed.

The degree of clinical improvement that occurs in the immediate post-operative period is conditioned entirely by the degree of structural disease in the hand and digital vessels where sympathetic tone is high. This stage of vasodilatation may appear clinically and on skin temperature measurement to be initially equal in all patients in whom nutritional lesions are absent. In some of these, however, this phase rapidly subsides during the ensuing week, and within two weeks spontaneous attacks of cyanosis may reappear. If careful hand blood flow studies are undertaken pre-operatively, such cases are invariably found to be associated with a diminished capacity of the hand to undergo vasodilatation. Rapid subsidence of vasodilatation to a degree at which cyanotic attacks spontaneously occur is thought to be due either to the presence of subclinical degrees of organic arterial disease or to an incomplete operation. Tracy and Simeone (1958) have shown in dogs that an incomplete sympathectomy may be followed by a degree of vasodilatation which is initially identical with that following a more complete surgical procedure, and the presence of known residual pathways may not be detectable for some time.

In cases in whom pre-operative blood flow studies have indicated that the capacity of the hand and digital vessels to dilate is normal, spontaneous attacks of cyanosis are not noticed by the patient until there is detectable evidence of a return of sympathetic nervous activity in the hands or digits. Such evidence has been shown by Haxton (1955) often to be initially sudomotor and this may precede detectable vasomotor activity by several weeks. Although the level of sympathetic activity and the time at which it returns may be influenced by the type of sympathectomy performed, it is seen earliest—at four months—in pre-ganglionic operations in which the line of section of the sympathetic chain has been below T.2 ganglion, and latest in cervico-dorsal ganglionectomy (Haxton, 1955).

Clinical effect of upper limb sympathectomy

Following an upper limb sympathectomy, and before sympathetic nervous control of the hand and digital vessels becomes re-established, there is a variable period of time during which considerable modifications of the vascular phenomena are apparent. These changes result both from the removal of vasomotor nervous control and the return of vascular tone. The effect in Grade 1 cases of the disease has already been discussed, while in Grade 2 patients the result, in the author's opinion, varies according to the degree of underlying structural disease of the arterial inflow. In the majority of cases, there is either complete abolition of the pallid phase of the syndrome or a change in its character from one which is painful and involves active constriction of arteries, arterioles, capillaries and venules to a form which is mainly passive and relatively painless. This type of pallor, which is comparable to that seen in Raynaud's phenomenon secondary to degenerative arterial disease, changes to cyanosis with dependency of the limb, and is induced not only

by local cold but also by activities such as car driving and the carrying of articles which requires active flexion of the digits against resistance.

Cyanosis in these patients is considerably decreased, although occasionally in some cases with a marked underlying structural arterial component it may persist for almost as long as it did pre-operatively. Pain, for which the operation is usually performed, is universally relieved, but in patients with prolonged cyanosis is replaced by an aching sensation of the digits which still constitutes some degree of residual disability.

In the third group of cases in which peripheral unhealed necroses are associated with organic occlusion of the digital arterial inflow, the nutritional lesions usually heal during the immediate post-operative period of vasodilatation, and in the author's experience remain healed in the majority of cases so long as vasomotor nervous control of the extemity remains absent. In subsequent years, however, when sympathetic nervous control becomes re-established, ulcers frequently recur and whereas during the first year following sympathectomy the digits remained free of necroses in 10 of 12 such patients, three years post-operatively further ulceration had developed in seven patients in this group.

The effect on scleroderma involving a single or several complete digits has been disappointing, as although in three of four such cases there followed a period of cutaneous vasodilatation lasting in one case as long as a year, it did not affect the cutaneous sclerosis or the patients' disability. Although it is not possible in such a small series to come to any conclusion as to whether true scleroderma, as distinct from sclerodactyly, should be regarded as a complication of primary Raynaud's disease, these cases have not been grouped under this latter diagnosis, as diffuse systemic collagen disease was subsequently found to be present in all.

The long-term effects of sympathectomy are dominated almost entirely by the return of sympathetic nervous control to the hand and digital vessels. Although the incidence of this varies both with the series reported and the post-operative interval at which the investigations are performed, in the author's series the long-term results are essentially comparable with the observations of Felder and his colleagues (1949), who found that in the 2–5 year period following sympathectomy, clinical recurrence and evidence of vasomotor nervous activity were present in approximately 80 per cent of cases (Table VII).

TABLE VII

EFFECT OF UPPER LIMB SYMPATHECTOMY ON THE SYMPTOMS OF PATIENTS WITH PRIMARY RAYNAUD'S DISEASE

Post-operative interval	*Nutritional lesions absent*			*Nutritional lesions present*		
	No symptoms	*Symptoms improved*	*No improvement*	*No symptoms*	*Symptoms improved*	*No improvement*
6–9 months .	4	11	2‡	0	10	2
3–5 years*† .	0	8	7	0	5	7

* 2 patients not traced

† Vasomotor nervous activity present in 22 cases.

‡ Vasomotor nervous control returned at 7 months.

The cause of this has recently been investigated by Haxton (1955), but whether it results from the regeneration or reorganization of sympathetic nerves remains obscure and controversial. The clinical deterioration that accompanies the return of sympathetic nervous control of the digital vessels is undoubtedly more pronounced in patients with primary Raynaud's disease than in other diseases treated by identical operative techniques. It is possible that this could be related to the nature of the underlying primary abnormality of the adrenergic neurotransmitter amines in Raynaud's disease, as this would result in both an apparent and an actual increase in vasomotor nervous control being present in these patients.

Despite these limitations, sympathectomy remains a most valuable method of treatment for patients with Raynaud's disease and will remain so until a more satisfactory, safe and effective long-term form of therapy becomes available.

Vasodilator drugs

Although it is not possible to deal individually with the very large number of vasodilator drugs available, observations on four of the short-acting ganglion blocking and adrenergic blocking drugs have not led to the conclusion that they are at the moment of any considerable value in the treatment of any except the mildest form of Raynaud's disease. The author agrees with Goetz (1959) that, as a group, vasodilator and sympathicolytic drugs have proved clinically disappointing.

The difficulties encountered in their clinical application arise mainly from the generalized nature of their action and the variation in the degree of blockade that they induce. Although there is no doubt that under in-patient conditions at a relatively fixed environmental temperature it is perfectly possible to induce a reasonably stable level of sympathetic blockade in the hands of patients with Raynaud's disease, it is far more difficult to maintain this under the out-patient conditions encountered in everyday life. Individual variation in sensitivity to the drugs, together with changes in the rates of intake, absorption and elimination of short-acting compounds result in a relatively unstable systemic circulation, and if this is coupled with the wide range of vasoconstrictor impulses that result from changes in posture and environmental temperature, it becomes easier to understand the limitations in their clinical application. In some cases under oral therapy, examined as out-patients, the degree of blockade was found at one time to be clinically ineffective, whilst at others to be of such a degree as to induce, in the erect position, a haemodynamic shift which would more than counteract the increased hand blood flow obtained from sympathetic inhibition. In other cases, even if a reasonably stable degree of vasodilatation had been obtained, the resultant heat loss from the hands on cold exposure, particularly in those patients with a low level of heat production, caused a lowering of body temperature, subjective coldness and severe attacks of shivering.

Although it would be erroneous to consider that these features preclude the use of all of these drugs in Raynaud's disease, they do introduce difficulties which in the author's hands have severely limited their clinical value.

Metabolic and endocrine treatment

Studies of the pattern of hand blood flow under a number of experimental conditions indicated that there are two main ways in which this can be modified to produce an increase over the lower temperature range.

The first of these, in which the degree of sympathetic nervous control of the hand and digital blood vessels is decreased, has already been dealt with. However, the difficulties associated with sympathectomy and the use of short-acting sympathetic blocking agents stimulated a search for a more stable long-acting compound whose activity could be maintained at a reasonably constant level for long periods of time in ambulatory patients.

The second, which evolved from the work of Roth and Sheard (1950), indicated that in patients in whom the level of tissue metabolism was raised as a result of increased thyroid activity, a degree of peripheral vasodilatation was present which was approximately related to the increase in the general metabolic rate (Peacock, 1960b).

The former, which focused attention on the use of reserpine, was allied eventually to the use of triiodothyronine and this resulted in two pilot studies being undertaken on patients with Raynaud's disease using these compounds.

Reserpine

Reserpine in a dose of 0·25 milligram three times a day was given orally to six patients with Raynaud's disease and its effect on their symptoms, signs and resting digital temperatures carefully analysed. Although in only two of these cases was the resting digital temperature raised, it was found to diminish considerably the intensity of the pallid phase of the phenomenon, but to have little effect in those patients whose metabolic rate was low or in whom cyanosis was a prominent feature of the attacks (Peacock, 1960c). It appeared from these studies that although reserpine would diminish considerably the initial degree of cold constriction, it had little effect on the recovery phase of the attack and did not materially affect the rate at which reactionary hyperaemia subsequently developed.

Triiodothyronine

The decision to use triiodothyronine in an attempt to induce peripheral vasodilatation by raising the level of tissue metabolism was considered justifiable in view of the low basal metabolic rates, the low level of serum protein bound iodine and the generalized cold sensitivity found in many patients with Raynaud's disease. Triiodothyronine was considered preferable to thyroid mainly because reports at that time suggested that a syndrome of hypometabolism existed in which cold sensitivity was present which could be benefited by triiodothyronine when previous thyroid therapy had failed (Freedberg, Kurland and Hamolsky, 1955; Kurland, Hamolsky and Freedberg, 1955; Tittle, 1956). The cause of this syndrome in which the thyroid function is dissociated from the metabolic rate of the individual is not known, but is generally considered to be due either to a peripheral under-sensitivity of the tissues, for a reason unknown, to circulating thyroid hormone (Reiss and Haigh, 1954), or to a defect in the transformation of thyroxine to a more active form (Freedberg, Kurland and Hamolsky, 1955). Although the endocrinology of this condition was not entirely comparable to that in Raynaud's disease, in which the serum protein bound iodine levels were in most cases subnormal, there appeared to be sufficient similarities to justify an experimental trial of triiodothyronine.

The effect of triiodothyronine, 20 micrograms four times a day, on the signs, symptoms, hand blood flows and resting digital temperatures, was analysed in six cases of Raynaud's disease in whom the metabolic rates were low. Four of these patients had relapsed following previous upper limb sympathectomies.

The result of this treatment in this group of patients was of considerable interest. Cyanosis, which had been a marked feature of the syndrome in these cases, was either completely abolished or shortened from periods of hours to only a few minutes. The intensity of the reactionary hyperaemia was increased and the rate at which it developed was extremely rapid. Under resting environmental conditions of 20°C. the hands in all cases remained warm, the resting digital temperatures being elevated by 8°–12°C. and the hand blood flows considerably increased. The effect on the pallid phase of the phenomenon was not immediately apparent, but subsequently it became established that if a sufficiently severe cold stimulus was given to these patients it would induce a sudden attack of pallor which was more acute in onset and of greater intensity than anything previously experienced. The duration of pallor, however, was short and recovery extremely rapid. The pallor involved active constriction of the digital arteries, arterioles, capillaries and venules, and appeared to be due to increased peripheral vasomotor activity.

It was apparent from these observations that the clinical signs and symptoms of patients with Raynaud's disease could be profoundly modified by raising the tissue metabolism with triiodothyronine. Whereas at a low metabolic rate the syndrome was one of prolonged cyanosis and the slow development of reactionary hyperaemia, at a higher metabolic rate pallor became dominant and cyanosis largely disappeared. Raising the metabolic rate by triiodothyronine, as Roth and Sheard (1950) observed, increased the rate of vasodilatation and shortened the period of recovery from cold in these patients, but if the cold was sufficiently intense, it resulted in an apparently increased degree of initial vasoconstriction which could temporarily overcome the higher resting hand blood flows.

The results of the investigations using reserpine and triiodothyronine indicated that although these drugs had different actions, they were in many ways complementary. Whereas reserpine decreased the intensity of initial vasoconstriction and pallor, triiodothyronine, by raising tissue metabolism, shortened the recovery phase and decreased cyanosis.

Reserpine and triiodothyronine

During a four-year period 38 patients with Raynaud's disease have been treated with either reserpine or reserpine and triiodothyronine. Fifteen of these patients had had previous upper limb sympathectomies and in 10 nutritional lesions of the digits were present. Five were treated with reserpine alone in a dosage of 0·25 milligram twice daily and 33 were treated with reserpine 0·25 milligram twice daily (+ 0·25 milligram) and triiodothyronine 20 micrograms four times daily (+ 20 micrograms). In 10 patients the vascular symptoms were completely suppressed so that there have been no further attacks of digital pallor or cyanosis. In 23 patients, although attacks of pallor and cyanosis still occur, they are less frequent and of shorter duration than those previously experienced, and under most environmental circumstances the hands remain warm. In 5 patients there has been no change in

either the vascular symptoms or the peripheral blood flow. In those cases in whom the symptoms were suppressed or improved, the change in the vascular condition was accompanied by a general and remarkable increase in bodily warmth, which was absent in the failed group of cases. When the endocrine state of the two groups was compared, the only significant difference lay in the lower level of urinary excretion of 17-ketosteroids in the failed group of cases (3·2 milligrams per 24 hours as compared to 6·4 milligrams per 24 hours). Experiments with depot testosterone indicated that the general level of tissue metabolism could be increased in such patients by androgen therapy and four of these cases were subsequently considerably improved by the use of methylandrostenediol.

Complications of reserpine and triiodothyronine therapy.—The complications of this form of treatment have been minimal. A third of the patients experienced a period of tiredness lasting 10–14 days accompanied by some swelling of the nasal mucous membrane. In all but two cases this was self-limiting and the more recent introduction of 10-methoxydeserpidine has largely eliminated this initial period of central depression. There has been no evidence of cardiac strain and the pulse rate either remains within the normal range or becomes slowed. The menstrual cycle has remained regular in all cases in which it was previously normal and there has been no constant pattern of change in either weight or appetite. In the winter months in some cases it has been necessary to increase the dose of triiodothyronine to 100 micrograms daily owing to the increased peripheral utilization that follows prolonged cold exposure (Dempsey and Astwood, 1943), whilst in summer the dose can either be decreased or dispensed with according to the severity of patients' symptoms. In such cases investigation of thyroid uptake using ^{131}I has confirmed the return of function to the individual's own thyroid gland.

Discussion

The use of reserpine in the treatment of patients with Raynaud's disease has previously been reported by Scalfi, Jacono and Iuliani (1956) and Reichert (1956). Although its action was originally considered to be mainly on the hypothalamic sympathetic outflow (Bein, 1955), it is now known that it causes not only a generalized loss of catechol amines throughout the body (Muscholl and Vogt, 1958) but also decreases the noradrenaline content of arteries (Burn and Rand, 1958). Experimentally in rats, reserpine has been shown to block some of the metabolic effects of triiodothyronine (De Felice, 1957) but its action in most cases of Raynaud's disease, as in thyrotoxicosis (Canary and his colleagues, 1957), appears to be more pronounced on the noradrenaline fraction of the sympathetic nervous system. Unless given in large doses it does not greatly reduce the increase in tissue metabolism induced by triiodothyronine which is possibly mediated by its potentiation of adrenaline. Although thyroid hormones as a group tend to potentiate adrenaline-induced vasoconstriction in isolated arteries (Smith, 1953), *in vivo* this is accompanied by a more rapid recovery due probably to the associated increase in tissue metabolism. It is an interesting scientific observation which is clinically disappointing that triiodothyronine will not change either the peripheral tissue metabolism or the hand blood flows of the completely sympathectomized hand. It would appear, therefore, that adrenaline or noradrenaline liberated from the adrenergic



FIG. 11.—Grade 3 primary Raynaud's disease: fixed cyanosis and sclerodactyly following four upper limb sympathectomies.

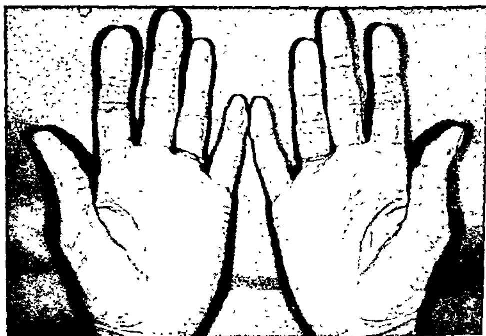


FIG. 12.—Hands of same patient as Fig. 11 after treatment for four years with reserpine, triiodothyronine and methylandrostenediol.

sympathetic nerve endings are essential as intermediaries for the peripheral metabolic action of triiodothyronine. The cause of the increase in metabolism that accompanies the use of androgens in patients with low 17-ketosteroid excretion levels is not clear. Clinically the androgens seem to sensitize such patients to triiodothyronine—a phenomenon previously observed in thyroid treated patients by Eidelsberg and Ornstein (1940).

Although it has become obvious that complete suppression of symptoms cannot be obtained in those patients with primary Raynaud's disease in whom structural arterial disease is a major component of the underlying vascular abnormality, this form of treatment has been of particular value both in the uncomplicated stages of the disease and in the treatment of patients in whom clinical relapse following an upper limb sympathectomy is associated with the return of vasomotor nervous control of the hand and digital blood vessels (Figs. 11 and 12). The present studies in which peripheral vasodilatation is induced by raising the level of tissue metabolism are still regarded by the author as being mainly experimental and other possible methods of raising tissue metabolism without a coincidental increase in vasomotor activity are being actively investigated. They tend to indicate that the hormonal and metabolic states of patients with vascular disease are of more importance than was originally appreciated, although the exact role of hormones in the treatment of vascular disease is still uncertain and requires further investigation.

SUMMARY

As a result of these investigations, primary Raynaud's disease is considered to be a vasospastic disease in which there is present an abnormality in the production or metabolism of adrenergic neurotransmitter amines liberated mainly, if not entirely, from the peripheral sympathetic nerve endings. The predilection of the disease for the upper extremities is thought to be due to the potentiation of the vasoconstriction induced by these amines by local cold.

The disability that results and the character of the presenting vascular phenomena are modified both by the degree of organic disease in the arterial inflow and the metabolic and endocrine state of the individual. The frequent precipitation or exacerbation of the disease by mental or physical stress suggests that, in such patients, it should be regarded as essentially a stress disease in which the hypothalamic regulation of sympathetic nervous activity and possibly the function of the pituitary gland is deranged.

REFERENCES

Allen, E. V. (1937). *Proc. Mayo Clin.*, **12**, 187.
— and Brown, G. E. (1932). *J. Amer. med. Ass.*, **99**, 1472.
Barcroft, H., and Walker, A. J. (1949). *Lancet*, **1**, 1035.
Bazett, H. C. (1949). *Amer. J. med. Sci.*, **218**, 483.
Bein, H. J. (1955). *Ann. N.Y. Acad. Sci.*, **61**, 4.
Burn, J. H., and Rand, M. J. (1958). *Lancet*, **1**, 903.
Canary, J. J., Schaaf, M., Duffy, B. J., and Kyle, L. H. (1957). *New Engl. J. Med.*, **257**, 435.
Ciba Symposium (1957). *Ciba Symp.*, **10**, 97.

Cooper, K. E., Cross, K. W., Greenfield, A. D. M., Hamilton, D. McK., and Scarborough, H. (1949). *Clin. Sci.*, **8**, 217.
De Felice, E. A. (1957). *Experimentia*, **13**, 323.
Dempsey, E. W., and Astwood, E. B. (1943). *Endocrinology*, **32**, 509.
Eidelsberg, J., and Ornstein, E. A. (1940). *Endocrinology*, **26**, 46.
von Euler, U. S. (1946). *Acta physiol. scand.*, **12**, 73.
Felder, D. A., Simeone, F. A., Linton, R. R., and Welch, C. E. (1949). *Surgery*, **26**, 1014.
Freedberg, A. S., Kurland, G. S., and Hamolsky, M. W. (1955). *New Engl. J. Med.*, **253**, 57.
Goetz, R. H. (1959). *Surg. Gynec. Obstet.*, **109**, 209.
Haxton, H. A. (1955). *Ann. R. Coll. Surg. Engl.*, **14**, 247.
Hunt, J. H. (1936). *Quart. J. Med.*, **29**, 399.
Kurland, G. S., Hamolsky, M. W., and Freedberg, A. S. (1955). *J. clin. Endocrin.*, **15**, 1354.
Lecoq, R., Chauchard, P., and Mazoué, H. (1952). *C. R. Soc. Biol., Paris*, **146**, 683.
Lewis, T. (1929). *Heart*, **15**, 7.
— (1938). *Clin. Sci.*, **3**, 287.
— and Pickering, G. W. (1934). *Ibid.*, **1**, 327.
Lynn, R. B., Steiner, R. E., and Van Wyk, F. A. K. (1955). *Lancet*, **1**, 471.
Mann, M., and West, G. B. (1950). *Brit. J. Pharmacol.*, **5**, 173.
Muscholl, E., and Vogt, M. (1958). *J. Physiol.*, **141**, 132.
Peacock, J. H. (1958). *Clin. Sci.*, **17**, 575.
— (1959a). *Ibid.*, **18**, 25.
— (1959b). *Circulat. Res.*, **7**, 821.
— (1960a). *Clin. Sci.* In the press.
— (1960b). Arris and Gale Lecture, Royal College of Surgeons.
— (1960c). *Lancet*, **2**, 65.
Peart, W. S. (1949). *J. Physiol.*, **108**, 491.
Raynaud, A. G. M. (1874). *Arch. gén. Méd.*, **1**, 5.
— (1862). *De l'asphyxie locale et de la gangrène symétrique des extrémitiés.* Paris; Thèse.
Reichert, F. L. (1956). *Amer. J. Surg.*, **91**, 41.
Reiss, M., and Haigh, C. P. (1954). *Proc. R. Soc. Med.*, **47**, 889.
Reynolds, S. R. M., and Foster, F. I. (1939). *J. clin. Invest.*, **18**, 649.
Ross, J. P. (1958). *Surgery of the Sympathetic Nervous System*, p. 51. London; Baillière, Tindall and Cox.
Roth, G. M., and Sheard, C. (1950). *Circulation*, **1**, 1142.
Scalfi, L., Jacono, A., and Iuliani, G. (1956) *G. Clin. med*, **37**, 1635.
Smith, D. J. (1952). *Amer. J. Physiol.*, **171**, 528.
— (1953). *Ibid.*, **172**, 118.
Tittle, C. R. (1956). *J. Amer. med. Ass.*, **162**, 271.
Tracy, G. E., and Simeone, F. A. (1958). *Surgery*, **43**, 125.
Whelan, R. F. (1951). *Observations on the Interaction of Chemical, Nervous, Thermal and Postural Factors in the Control of the Peripheral Circulation*, p. 360. Belfast; M.D. Thesis.
Wickbom, I., and Bartley, O. (1955). *Acta radiol., Stockh.* Suppl., **128**, 438.

SELECTED ABSTRACTS—VASCULAR DISEASE

Vascular reactivity

Clinical aspects

Clinical aspects of vascular reactivity are discussed by GOETZ (1959). It has been shown by recent work that there are significant differences in the vasomotor control of different areas of the skin, such as the hand and the forearm. Investigators have demonstrated

that during sweat gland activity a bradykinin-forming enzyme appears in the sweat and bradykinin (a polypeptide with vasodilator properties) appears in the skin. As the presence of an active vasodilator mechanism on body heating in the vessels of the hand or fingers has not been proved, it is considered that vasodilatation in the hand is the result of release of vasoconstrictor tone only. A vasodilator supply of skeletal muscle does not appear to be involved in blood pressure control, but may play a role in so-called alarm reactions; evidence of its existence in man is not definite and it seems to be involved in the reaction to fainting. The vasodilatation of skin, and sweat secretion, are more interrelated than previously supposed, and are not functionally independent and of separate peripheral neural control: although both skin and muscle vessels are innervated by sympathetic fibres, the vasomotor centres controlling them can function independently. Reflex activity of skin vessels serves mainly as a body temperature control and blood pressure homeostasis, whereas reflex activity of the muscle vessels is involved in the control of the haemodynamic changes occurring with changes in posture. There have been many examples of spontaneous changes in vascular tone resulting from central tonus adjustments affecting skin vessels, and recent investigators have demonstrated spontaneous rhythmic changes in the muscle circulation. The peripheral blood flow in organic arterial disease may be compromised by even slight changes in blood pressure; in bleeding, for example, even slight changes in vasoconstrictor tone may produce a shut-down in certain areas; the shut-down associated with an arterial embolus usually attributed to severe vasomotor spasm is explained by the fall in intra-arterial pressure distal to the block below the critical closing pressure. In the treatment of occlusive arterial disease, because of the central depressor and dilator effects of vasodilator drugs blood may be shunted from the diseased area to other areas, and the therapy may achieve the opposite of what was intended. The control of venous tone does not necessarily run parallel to arterial vasomotor control in certain areas; evidence of a venivasomotor reflex has included the so-called afterdrop seen in the plethysmogram following venous occlusion. In the skin, the principle concerning vasa privata versus vasa publica is exemplified by division of blood flow into nutritive capillaries and arteriovenous anastomoses controlling body temperature. A return of vascular (not vasomotor) tone has to be contended with after a limb has been completely sympathectomized; it seems that the smooth-muscle cell has an inherent basal tone, predominantly dependent on local factors.

Peripheral vascular grafts

Experimental comparisons

Dale and Mavor (1959) discussed peripheral vascular grafts and compared autogenous veins, homologous arteries and synthetic tubes. Five years of experimental grafting in dogs has shown that the procedure can be accomplished with several materials, but that peripheral grafting is more difficult than aortic and a more severe test of the grafting material. Materials and methods are described. Of 42 autogenous vein grafts, 16 were thrombosed prior to sacrifice of the dogs, 26 were either found open at necropsy or shown to be so by arteriogram post-operatively. The grafts varied from 5 to 10 centimetres in length and were placed end-to-side between the proximal and distal superficial femoral artery, except for five iliofemoral shunts. Of 43 homologous arterial grafts placed in the same positions, 14 thrombosed while 29 remained patent. Sixty-eight synthetic tubes were placed as grafts either between the aorta, the iliac or femoral artery and a more distal vessel. The six synthetics used included "Fluflon" dacron, crimped nylon, Schlegal nylon, Teflon tubes, the "Ethigraft" dacron tube and sheet orlon. Of these, "Fluflon" dacron was the easiest to place and suture and conformed best to the host-bed. Experiments with the three grafts totalled 153, excluding aortic replacements. The patency rate for autogenous veins was 64 per cent, for homologous arteries 77 per cent, and for the various synthetics 29 per cent, the poor results of the last resulting from deposition of a relatively thick neo-intima in the tube. Microscopic study indicates that autogenous venous grafts persist as living tissues, with thickening of the venous wall. Arterial homografts, however, eventually become fibrous, with broken elastic

Cooper, K. E., Cross, K. W., Greenfield, A. D. M., Hamilton, D. McK., and Scarborough, H. (1949). *Clin. Sci.*, **8**, 217.
De Felice, E. A. (1957). *Experimentia*, **13**, 323.
Dempsey, E. W., and Astwood, E. B. (1943). *Endocrinology*, **32**, 509.
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— (1959a). *Ibid.*, **18**, 25.
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— (1960b). Arris and Gale Lecture, Royal College of Surgeons.
— (1960c). *Lancet*, **2**, 65.
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fibres and degenerative changes in the smooth-muscle layer. While dilatation and aneurysm formation may occur in an aortic replacement by an autogenous vein, it is unlikely when the vein replaces a smaller peripheral artery, because of the lower tension on the wall of the replacing vein. The outcome of these experiments has changed clinical policy from the use of homologous arteries to that of autogenous veins for peripheral shunt replacement of atherosclerotic lesions of the femoro-popliteal system. Early results in 28 cases have been satisfactory, an initially patent graft being secured in 21 of these patients.

Synthetic arterial grafts

Improved crimped graft of Teflon

Progress in synthetic graft development is discussed by EDWARDS (1959). The first essential in obtaining a safe, simple, durable and versatile synthetic arterial graft is to determine the superior fibre, and then to ascertain the most desirable method of producing such a graft. An evaluation of various materials has demonstrated the superiority of Teflon: it fulfils all the principal criteria and absorbs no water; an additional property is its flex abrasion resistance. The slippery feel of the yarn is indicative of lack of water absorption and is the cause of the low flex abrasion. Another advantage of Teflon grafts is the much greater rapidity with which the fibrin neo-intima heals and becomes attached to the inside. Seamless tubes can now be readily produced by weaving, braiding or knitting, and have the advantage of avoiding wrinkling. In the production of a tube end that can be sutured, a knitted tube is superior to woven or braided tubes; as it is fabricated of interlocking stitches it is almost impossible to make it fray, and a hole can be cut in the side of the tube for a branch without ravelling. The production of minimum but adequate porosity is achieved in cylindrical tubes by a process of tight-weaving; tubes made in this way can be implanted without pre-clotting or the risk of blood loss. The prevention of kinking is best achieved by the incorporation of corrugations or crimps; experiences with animal experiments and clinical cases have shown that shallow corrugations do not increase the danger of thrombosis, even in small grafts, and are quite satisfactory in preventing kinking across areas of flexion. Recent work has shown also that angulation of a branch is not dangerous if a relatively non-collapsible flexible crimped tube is used. As there is no chemical method of setting corrugations in Teflon, a high temperature bake is used instead. The author now uses woven crimped Teflon tubes, and has found that these low-porosity tubes have the advantage of being safe in hypertensive patients, in those with possible clotting defects and in cases in which heparin has been used.

Occlusive disease of innominate, carotid, subclavian and vertebral arteries

Surgical considerations

DE BAKEY (1959) and his colleagues discussed surgical considerations of occlusive disease of innominate, carotid, subclavian and vertebral arteries. A study has been made of 174 patients with manifestations of arterial insufficiency of the cerebrum and upper extremities. Arteriographic examination revealed the presence of extracranial arterial occlusion in 73 patients: 63 of whom were operated upon. In 10 of the 63 patients the lesions were found to be inoperable because of extensive complete occlusion of the internal carotid and vertebral arteries without a patent distal segment. In the remaining 53 cases the lesions were segmental and susceptible to restorative operations. Treatment generally was of two types, endarterectomy and end-to-side by-pass graft. The former was used for lesions that were discrete and well localized to a relatively short segment of artery, and the latter for more extensive lesions, using a specially designed flexible knitted dacron tube. Application of these procedures depended largely upon the location of the lesion. Lesions in the great vessels arising from the aortic arch were operable, regardless of location and extent of occlusion; incomplete occlusions of the internal carotid and vertebral arteries were similarly operable; complete occlusions of the latter vessels were seldom operable unless explored soon after the onset of symptoms;

cases in which the occlusion was of long duration also were regarded as inoperable. The main manifestations of the disease were arterial insufficiency of the cerebrum and upper extremities in cases of proximal occlusion and cerebral arterial insufficiency in the distal occlusions. The success of these surgical operations depends upon various factors in addition to the restoration of circulation. These factors include especially, anaesthesia, control of peripheral arterial blood pressure, and measures to prevent cerebral ischaemia during temporary arrest of the cerebral circulation. In most cases with moderate to severe neurological disturbances, in which the lesion is usually located in the internal carotid or vertebral arteries, local anaesthesia is preferable; in cases with proximal occlusive lesions there is usually adequate collateral cerebral circulation. For this reason and because thoracotomy is usually necessary, light general anaesthesia is used; hypothermia or temporary shunts during arterial occlusion are unnecessary unless carotid compression pre-operatively, or temporary carotid occlusion during operation, produced cerebral disturbances. Restoration of a pulsatile circulation was achieved in the treatment of 72 lesions. There were three deaths from irreversible ischaemic brain damage in patients with cerebral arterial insufficiency present pre-operatively, two from myocardial infarction following operation and one from haemorrhage. Observation of surviving patients for over five years showed that the successful results of surgery have been well maintained.

Occlusive vascular disease of the legs

The case against vasodilator drugs

GILLESPIE (1959) presents the case against vasodilator drugs in occlusive vascular disease of the legs. Although vasodilator drugs are generously prescribed in obliterative vascular disease, their therapeutic value is very doubtful. To relieve rest-pain or ischaemic skin lesions, they must increase blood flow in the foot; to relieve claudication, they must increase muscle blood flow in the calf. Their effect should be localized in the diseased limb, their action should be prolonged and they should be effective when given by mouth. These principles are examined and the methods described. The drugs used were Priscol, Dibenyline, Largactil and promazine. In healthy limbs, the blood flow invariably increased with their administration, justifying their use in ischaemic disease. In 10 of 15 patients with unilateral occlusion, however, the foot blood flow in the affected limb was actually reduced by the drug. In all cases it increased in the more normal limb. In three of seven cases of bilateral occlusion, it was reduced in both limbs. These results suggest that vasodilators, generally considered harmless, can seriously reduce an already poor blood flow to the foot. When the drug is given orally or intravenously, vasodilatation is general and blood is redistributed; but, owing to the arterial occlusion, that destined for the diseased limb can easily pass elsewhere. Thus the blood flow beyond the obstruction may actually be reduced. If the systemic blood pressure is also lowered, filling of the arterial tree distal to the block may be further reduced. Vasodilators, then, have no place in the treatment of acute arterial occlusion or the chronically ischaemic foot. The relief of claudication depends upon increased muscle blood flow on which vasodilators have as little effect as sympathectomy. In a case of bilateral calf claudication and arterial occlusions, the blood flow in both foot and calf was reduced. To prescribe vasodilators, therefore, is useless. Their supplementary action after sympathectomy is ineffective. The response to a vasodilator drug, has also been suggested as a useful indication of the probable effect of sympathectomy but as a pre-operative test it is valueless and may lead to a suitable patient being refused operation.

Experimental gradual arterial occlusions

In vitro *and* in vivo *observations*

LITVAK and VINEBERG (1959) presented a study in experimental gradual arterial occlusions with *in vitro* and *in vivo* observations. In the first experiment dicetyl phosphate-coated cellophane was wrapped round peripheral arteries in dogs. In the second experiment, the rate of swelling of casein plastic material *in vitro* was examined; in the third

and fourth experiments, this material was used on peripheral and coronary arteries. Twelve mongrel dogs were used. Strips, four centimetres in width, were applied to the right carotid and left femoral arteries, two centimetres wide to the left carotid and the left brachial and one centimetre wide to the right brachial arteries. The vessels were re-explored at 2–60 days intervals for three tests of occlusion: (1) palpation for arterial pulsations proximal and distal to the cellophane wrapping; (2) transection of the arteries distal to the wrapping to observe blood flow through the wrapped segment; and (3) removal of the segments and their attachment to an apparatus producing a constant saline flow. Arterial pulsation persisted proximal and distal to the cellophane strip. Every vessel bled freely after distal transection. None of the segments diminished the blood flow. Since no significant occlusion of any artery was produced, casein plastic material in the form of a sleeve, with an eccentrically-placed lumen, was employed. This expanded in all dimensions with negligible narrowing of the lumen. Massive inflammatory reaction discouraged further use. Similar sleeves, 25 millimetres long, with central lumina and encased in stainless steel, were applied to the carotid and femoral arteries of 12 dogs. Gradual narrowing of the arteries occurred over periods of time varying with the luminal diameter of the sleeve. In four dogs, sleeves eight millimetres long, were applied to the same arteries. The arterial pulse weakened and the blood flow diminished sooner than with the 25-millimetre sleeve, while arterial occlusion occurred almost a week earlier. Microscopic and gross observations suggested that occlusion was produced by mechanical narrowing of the vessel due to hygroscopic swelling of the plastic, fibroblastic reaction in the arterial walls and intraluminal thrombosis arising from the intima. Casein plastic sleeves five millimetres in length and six millimetres in diameter, cased in stainless steel, were next applied to major branches of the left coronary artery in 12 dogs. All died within 4–26 days after thoracotomy with progressive coronary artery occlusion and myocardial infarction. External diameters of arteries diminished directly with the time of sleeve application. At 25 days, a minute opening marked the arterial lumina; none was completely occluded.

Abdominal aortic aneurysm

Results of treatment by resectional placement of homograft

The late results in 110 patients with abdominal aortic aneurysm treated by resectional placement of aortic homograft are recorded by SHERANIAN, EDWARDS and KIRKLIN (1959). Among the 110 cases there were 104 elective and 6 emergency operations: in 11 cases the operations were performed too recently for a significant follow-up; the remaining 99 cases have been followed up for periods of from six months to four years. The method of securing and preparing the homografts was basically the same as those using refrigeration with balanced electrolyte and nutrient solution. Grafts taken non-aseptically were sterilized in a solution of *beta*-propriolactone; the majority were taken aseptically and placed in a storage medium containing Ringer's solution, serum, and merthiolate, and refrigerated at 2°–4° C. until used; any vessel not used after five weeks of storage was discarded. There were 18 hospital deaths among the total of 110 patients: there were 3 deaths among the 6 emergency cases and 15 among the 104 cases without rupture of the aneurysm; the overall operative survival rate was 83·6 per cent. The causes of death were as follows: (*a*) related to grafting 8—rupture of graft 5, (presumed) failure of suture line 3; (*b*) not related to grafting—acute renal failure 3, intestinal infarcation 1, myocardial infarction 1, pulmonary embolism 1; (*c*) prolonged shock—rupture of aneurysm, emergency operation 3. The rupture of the wall of the graft, which is the primary serious complication of homografts in the abdominal aorta, has occurred both early and late in the post-operative period. It is possible that plastic prostheses may prove to be an advantage in avoiding the problem of graft failure which is experienced when homografts are used. An interesting feature is that all the three grafting failures which caused late deaths presented as severe gastro-intestinal haemorrhage. In one case the patient died suddenly at home, in a condition resembling shock, vomiting large quantities of fresh blood, 2½ years after the grafting, and necropsy showed the gastro-intestinal tract to be full of blood. A rupture of the wall of the graft had resulted

in a false aneurysm and death was caused by rupture of the false aneurysm into the retroperitoneal duodenum. The three-year survival rate of the series was 70·7 per cent compared with 49·2 per cent in an untreated series (Estes, 1950).

Coarctation of the abdominal aorta

D'ABREU, ROB and VOLLMAN (1959) described coarctation of the abdominal aorta. The condition is being recognized much more frequently of late though many cases had been treated for years as essential hypertension before the peculiar distribution of the arterial blood was recognized. Very often the hypertensive trouble is confined to the upper part of the trunk while the blood flowing to the lower is inadequate. Hence intermittent claudication may occur and surprise may be felt when sympathectomy produces little or no effect. The defects of development may be segmental or hypoplastic. A narrowing above or below the renal arteries accounts for three-quarters of the cases, while the hypoplastic and more extensive abnormality may also begin above or below the renal arteries and account for the remaining cases. If an arterial collateral circulation can be found below the diaphragm there is strong evidence that the abnormality is present while an arterial murmur may be heard over the abdomen or in the lower back. With so much of the blood circulation in the upper trunk the patient may complain of headache, vertigo and even of symptoms suggesting migraine. It is clearly desirable to exclude some other cause for partial or complete occlusion of the aorta and to be able to explain the hypertension in no other way before the diagnosis is accepted. Operative intervention may be designed to remove the narrowed part of the vessel and make an end-to-end anastomosis or repair in some other way. A by-pass operation may be desirable and if some vessels have to be clamped for a considerable time hypothermia or another and temporary by-pass may be needed. The splenic artery may be used and the authors illustrate various methods of doing this. It may be brought up to the cranial end of the normal aorta or down to the caudal end depending on the location of the stenosis. Several cases treated in this way experienced a great relief of the hypertension in the upper part of the body when a homologous aortic or arterial transplant was used and somewhat less relief when the splenic artery was employed. The spleen must naturally be removed. It is evident that in many cases in which this deformity is present it is the disturbed circulation of the kidneys which causes the hypertension. Patients usually complain mostly of ischaemic symptoms in the legs and it is in the elucidation of these that the abnormalities in other parts of the circulation are found. Aortograms should always be used to clinch the diagnosis. In most of the hypoplastic deformities the operations already described cannot be executed and only sympathectomy remains as an ineffective intervention.

Varicose veins

External saphenous vein

Varicosity of the external and pseudo-varicosity of the short (external) saphenous vein is discussed by DODD (1959). A review has been made of the condition, based on more than 90 operations on the short saphenous and varicose popliteal tributaries. The termination of the short saphenous vein is variable; KOSINSKI (1926) has described a "normal" a "high" and a "low" ending. Assistance in locating the termination is provided by (1) palpation in the popliteal space and calf, especially when the knee is slightly flexed; (2) use of the stripper; and (3) venography. Through the connexions of the long and short saphenous veins the hypertension in one incompetent system can pass into the tributaries of the other, and make them varicose, although the terminal valve of that saphenous vein is sound; the varicose long saphenous vein distends the short saphenous tributaries more frequently; this may render a "spot" diagnosis based on the distribution of the varices wrong or incomplete. As the area drained by the short saphenous vein is much smaller than that of the long saphenous vein, varicosity causes the effects of hypertension to fall on a relatively limited area, and there are consequently more ill-effects than follow varicosity of the long saphenous vein. Varicosity of the short

saphenous vein is diagnosed by inspection, palpation, digital percussion, and tourniquet tests. A cough impulse is seldom felt, but if it is present the author considers that it indicates incompetence of the valves of the iliac, femoral and popliteal veins. The state of the short saphenous vein is known from the tourniquet test, and the short saphenous "exclusion" test is used to prove the competence of the long saphenous and Hunter's canal communicating vein, by digital pressure at the popliteal space. As occasionally both the long and short saphenous veins are incompetent in a limb, or there is varicosity of the long saphenous vein in one limb and of the short saphenous vein in the other, both legs are tested. The name pseudo-varicosity of the short saphenous vein is given to varicose tributaries of the popliteal vein because their signs are similar to those of the faulty short saphenous vein. The main incompetent tributaries of the popliteal vein are the gastrocnemial veins; from experience with the present series the author considers that when gastrocnemial tributaries are varicose, they "surface" at the popliteal space, the calf, and at the gastrocnemius-tendo Achillis junction. If they are unligated some varicose veins may persist after sapheno-popliteal ligation and stripping, but this may be remedied by exploration of the popliteal vein and ligation of the faulty vessels. The results have been good in 86 primary cases and 6 recurrent cases.

REFERENCES

D'Abreu, A. L., Rob, C. G., and Vollman, J. F. (1959). *Arch. klin. Chir.*, **290**, 521.
Dale, W. A., and Mavor, G. E. (1959). *Brit. J. Surg.*, **46**, 305.
De Bakey, M. E., Crawford, E. S., Cooley, D. A., and Morris, G. C. Jnr. (1959). *Ann. Surg.*, **149**, 690.
Dodd, H. (1959). *Brit. J. Surg.*, **46**, 520.
Edwards, W. S. (1959). *Surgery*, **45**, 298.
Estes, J. E. Jnr. (1950). *Circulation*, **2**, 258.
Gillespie, J. A. (1959). *Lancet*, **2**, 995.
Goetz, R. H. (1959). *Surg. Gynec. Obstet.*, **109**, 209.
Kosinski, —. (1926). *J. Anat., Lond.*, **60**, 131.
Litvak, J., and Vineberg, A. (1959). *Surgery*, **46**, 953.
Sheranian, L. O., Edwards, J. E., and Kirklin, J. W. (1959). *Surg. Gynec. Obstet.*, **109**, 309.

A CANCER RECORDS BUREAU

A Review of the Work (1952-59) and its Implications

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NATIONAL REGISTRATION

Although the deductions in this article are based mainly on work carried out in the South Western Region of England, it is proposed in the first instance to deal with cancer registration throughout the country as a whole.

For this purpose, the contribution by the General Register Office on Cancer Registration in England and Wales to the World Health Organization and the Annual Report of the Chief Medical Officer of the Ministry of Health have been used.

Introductory

The primary objectives of the National Cancer Registration scheme in England and Wales, in which 800,598 cases had been registered to the end of 1958, are to obtain information about the incidence of cancer according to the site of the primary growth and about the period of survival of patients suffering from cancer. The scheme is based on voluntary registration of cases by hospitals and there is no payment for cases registered.

Responsibility for national registration now rests with two Government departments—the Ministry of Health and the General Register Office. The registering hospital is normally responsible for obtaining follow-up reports on each patient for a period of 15 years or until the patient's death. Some provision is made for supplementing this procedure by reference to death certificate registrations.

Historical

Cancer registration was begun in 1930 by the Radium Commission, which was established in 1929 to control the supply of radium to radiotherapy centres and to evaluate the use of radium in the treatment of cancer. The centres were required to supply the Radium Commission with information about cases treated with radium and about their subsequent condition. Statistical analyses based on this information were included in the Reports of the Commission from 1935.

A step towards expanding registration was taken in 1939 when a Cancer Act was passed in Parliament requiring the council of every county and county borough in England and Wales to make arrangements for adequate facilities for treating

cancer cases in their area. The Ministry of Health advised the councils that, among other things, they should provide for keeping records of treatment and its results in a standard form. However, the collection and analysis of records was suspended during the war.

In 1944, the Ministry of Health issued specimens of registration and case abstract cards, which were prescribed for use in all areas where a cancer scheme, which was approved by the Minister, was operating.

At the end of the war the Radium Commission introduced a similar system of record cards in its radiotherapy centres, and was nominated temporarily as the statistical bureau for the collection and analysis of all cases of cancer registered. Under the provisions of the National Health Service Act, 1949, the Cancer Act was repealed and the Radium Commission ceased to exist.

The continuation and extension of local arrangements for cancer registration became the business of 14 Regional Boards (now 15 by the addition of the Wessex Board in April, 1959) and of the Boards of Governors responsible for the administration of the teaching hospitals. There is no compulsion on them to make such arrangements. Later in this article, details are given of the work carried out under each of the Regional Boards, together with the numbers of the cases registered.

The General Register Office, the central Government department responsible for vital statistics, had already taken over the duties of statistical control and analysis in 1947.

Cases registered

Hospital boards have been encouraged by the Ministry of Health to arrange for registration of all cases of suspected cancer which are referred to hospital for treatment or advice. In nine of the 15 Regional Boards, cancer registries have been set up and three Boards have combined in one scheme.

In some regions, where registration is thought to be nearly complete, an attempt, in collaboration with the General Register Office and general practitioners, is now being made by use of death certificates to register all cases which did not attend hospital. In the other six regions, hospitals are still registering cases direct with the General Register Office but in four of them cancer registries are being planned (some of these have now been established).

The total number of cases registered in each year since 1954 and subsequently confirmed as cancer are as follows:

1954 ..	63,271	1957 ..	82,261
1955 ..	64,150	1958 ..	90,820 (provisional)
1956 ..	72,654		

As a result of the way in which the National Registration scheme developed, registration has always been more complete for cases receiving radiotherapy but this bias is gradually being reduced and has been eliminated in some regions.

Because the problems facing different hospitals have been varied and because the decision whether to organize registration in a region rests with the hospital boards, the relative completeness of registration of cases of cancer varies greatly from one region to another.

In some regions the registration of hospital cases is now complete; in others schemes are being introduced for complete registration of hospital cases; while in still other regions individual hospitals or groups of hospitals may register cases, even though there is no regional scheme.

Information collected

Details of the information collected centrally are indicated on "abstract cards". They fall into five categories—personal information about the patient, information about the growth, the period which elapsed before treatment, methods of treatment, and period of survival.

Some centres record and analyse information in greater detail than that collected centrally (*see* below).

Recording methods

The detailed arrangements for recording the information required vary considerably from one region to another but the essentials are common to all participating in the schemes.

When a patient enters hospital with suspected cancer, or as soon as cancer is suspected, a "registration card", recording essential details for identifying the patient, is made out normally by the hospital records officer. These cards are sent monthly to the regional centre if there is one, or to the General Register Office.

The registration cards have three main uses—to identify duplicate registrations, to ensure that an abstract card is submitted for every case confirmed as cancer and to record the movement of abstract cards. These duties are carried out by the regional centres, or by the General Register Office for hospitals not covered by a regional organization. If a case is found to be non-malignant before an abstract card is completed the regional centre or the General Register Office, as appropriate, is informed and an abstract card will not be completed.

The registering centre or hospital is responsible for checking the patient's condition by examination, or by correspondence annually after the date on which treatment was commenced (or, if no treatment was given, on the date of admission or first attendance). After the first annual "follow-up" the abstract card should be completed and all abstract cards relating to a particular year should be sent to the General Register Office—on dates specified by that Office.

The information on the abstract card is checked at the General Register Office for completeness, consistency and so forth and is then coded and transferred to punch cards. The "live" abstract cards are then returned to the registering centres for insertion of further follow-up information in due course. The abstract cards are again returned to the General Register Office at certain intervals; each time they are returned new punch cards are prepared relating to the up-to-date position.

Links with death certificate registration

This question is dealt with on page 63.

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patients had started as far back as 1945. This was carried out under the Radium Commission quite separately in two areas, the one centred in Bristol and the other in Plymouth.

When the National Health Service came into being the responsibility for the registration of cancer patients passed into the hands of the Regional Hospital Board. A single director was appointed for the whole region but, for geographical reasons, the two offices remained and it was arranged to appoint cancer clerks at Exeter, Torbay and Redruth. These clerks register their patients ultimately at the Plymouth office. The organization at the various centres throughout the country varies. Sometimes a clinician is in charge, sometimes a radiotherapist and sometimes a records officer, who refers problems to a medical adviser. This variety of organizations is, obviously, not in the best interest of cancer registration.

The area of England covered by the South Western Regional Cancer Records Bureau and the two areas—northern and southern—with offices at Bristol and Plymouth is shown in Fig. 13.

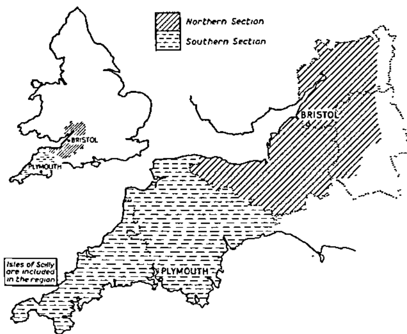


FIG. 13.—The area covered by the South Western Board extends from Tewkesbury to the Isles of Scilly and includes the administrative counties of Cornwall, Devonshire, Gloucestershire, Somerset and Wiltshire (except the parts included in the South West Metropolitan Regional Hospital Area and the Oxford Regional Hospital Area); the Isles of Scilly; the county boroughs of Bath, Bristol, Exeter, Gloucester and Plymouth, and so much of the administrative county of Dorset as comprises the Borough of Lyme Regis.

At each of the two offices, there is a highly efficient cancer records officer, whose great importance is emphasized, for they should have a full knowledge of

Staff and finance

The memorandum of the General Register Office to the World Health Organization goes into details on the subject of staff and finance. Needless to say, there is great variation from region to region but it is estimated that, in a centre where registration is well organized, the cost of registration and follow-up amounts to about 13 shillings per case.

The officers of the General Register Office work in close collaboration with the Ministry of Health.

Tabulation

The main objectives of tables prepared are to show the incidence of cases registered by site, sex and age and to show survival rate after 5, 10 and 15 years from registration.

The first study based on cases registered in 1945 and 1946 were published in a special study (Stocks, 1950) directed largely to maintaining and stimulating interest. Because these were the first years from which figures from the national scheme were available, three-year survival rates were later published as a supplement to this study (General Register Office, 1952).

Figures of cases registered in 1947 and 1948 have been published in a supplement to the Registrar General's Statistical Review (1949) and a further supplement giving five-year survival rates for cases registered in 1945 and 1946 was subsequently published (Registrar General's Statistical Review, 1950–51). A further report was published in 1957.

CANCER REGISTRATION IN A REGIONAL BUREAU

Confidentiality

Some time ago, the Ethical Committee of the British Medical Association decided that cancer should be an exception to the rule of confidentiality. Hospitals and general practitioners send the details of all their cancer patients to the Regional Bureau without the permission of the patient. It was felt, quite rightly, that if a patient had to be informed of the nature of his disease, the whole organization of cancer registration would break down.

Organization

Cancer registration centres are gradually being established throughout Great Britain, but it is a slow process and it will be some time before full registration on a national basis will be attained. There are still members of the medical profession who do not appear to appreciate the value of cancer registration. It is almost inconceivable that these doctors do not seem to realize that, unless we know accurately how many patients are suffering from cancer, the sites at which it occurs, the methods of treatment and the results of such treatment in detail, we cannot even begin to assess the incidence of the disease or the overall results of treatment at any one time.

In the South Western Region we were fortunate in that registration of cancer

Relations with the General Register Office

It has always been one of the main functions of the Bureau to register all notified and suspected cases of cancer with the General Register Office. We are thus able to play our part in the scheme of National Cancer Registration. Our figures are available to the Ministry of Health and have been used by the Chief Medical Officer in his annual report.

Recently the Bureau has undertaken to produce details for a special survey of lung cancer cases covering a period of six months.

Proposed liaison with cancer centres in the United States of America

Arrangements are being made for a liaison between histologists in Connecticut and in the South Western Region for the study of methods of assessment of cases of carcinoma of the cervix uteri.

It is also suggested that a statistical liaison be established between the South Western Region and Connecticut—the population of the two regions being approximately the same.

Progress in cancer registration

We have now reached something like 100 per cent cancer registration and with information received from the General Register Office, our figures are nearing completion (*see* below).

Most hospitals deal direct with the Bureau, and sometimes registration is effected through the parent hospital. Our experience is that the standard of record keeping and of the clinical notes of the surgeons is very high; this applies to hospitals both large and small. One or two hospitals appear to be unable to organize their records departments and a few of them appear to lose interest in their patients after discharge. The records of the radiotherapy departments are and have always been exemplary.

Death certificate returns

The Bureau receives each week a return from the General Register Office giving the details of all those patients who have died of cancer and whose death certificates have been transmitted to the General Register Office.

A careful survey of these returns has proved helpful to us in many ways. Often we have been able to identify patients who have been treated in hospital but who have not been registered with us. The number of these patients is not great but the check on the hospitals has been invaluable.

Our records show that there are still many patients who die of cancer without ever being in hospital. Many of these patients are registered on death certificates only. It is surprising that, in the year 1958, the number of these patients is no less than 1,786 (one less than in 1957). Most of these patients are aged over 70 years.

record keeping and should be able to train cancer clerks. Again, these clerks must be hand picked and must be made to understand the very confidential nature of their work. The strain of dealing with records of hundreds of cancer patients may tell on a sensitive person and the clerks must be carefully watched when they start work in the Bureau. In a few instances, where the hospital records departments are understaffed or inefficient, it may be necessary to send out clerks from the central office to help them out. This practice is discouraged; most hospital records officers are well able to deal with cancer cases in the course of their ordinary work and to pass on to the Bureau the essential details of such patients.

The patients are, usually, followed up by the hospitals and the information passed on to the Bureau for entry on the patient's case sheet and his abstract card. Often, it is necessary for the Bureau to remind the hospital of the dates of follow-up. Where indicated, the general practitioners are asked how the patients are getting on and this information is also entered. Now and again, more than one reminder is needed.

It is vital for the Bureau to set out deliberately to get into friendly relations with the hospitals, the records officers and the medical staff and, of course, with the general practitioners. In the South Western Region, the hospitals as a whole and the general practitioners have always been most co-operative.

One weak spot in the scheme is the records of private patients but many surgeons let us have the requisite information about them.

In the early days of the formation of a cancer registry, it is wise for the Director to make a round of the hospitals and, where possible, to get into personal touch with the general practitioners. One excellent way of doing this is to embark on some particular survey of statistics—for instance, of cancer at one site in the body. This enables the Director to get in touch with both hospitals and doctors.

A very complete card index system is maintained by the Bureau. This is available at any time for special surveys and every patient registered is included in the index. It is frequently used to answer queries from doctors or hospitals in connexion with cancer—such as incidence at special sites, results of treatment and so forth—and this can be done with the minimum of delay. Table I gives figures showing the work of the Bureau.

We are able to offer temporary accommodation to statistical research workers.

Population

The population of the South Western Region is 2,805,000; of which 1,364,000 are males and 1,441,000 are females. This is a very convenient unit of population to work with.

TABLE I

FIGURES SHOWING THE WORK OF THE BUREAU

Number of cases registered to the end of 1958 . . .	84,706
Number of new cases registered in 1958 . . .	9,605
Number of cases followed up in 1958 . . .	19,535

Under each site, an analysis of the cases who have survived ten years is given. This analysis deals only with treated cases. Under each site are also given tables showing the number of cases registered in the years 1949-1953 showing the 5-year survival rate.

The Tables which follow have been taken from the report in order to demonstrate their style. There are 39 such tables covering the sites of cancer throughout the body.

TABLE II

MALIGNANT GROWTHS OF TONGUE (*I.S.C.* 141)

	Total cases			*Treatment*								*Unrelated Deaths*
				All cases				*Survivors*				
	Reg'd	*Treated*	*Alive*	*Surg*	*Surg+*	*x-rays*	*Rad*	*Surg*	*Surg+*	*x-rays*	*Rad*	
								5-Year Survivors				
1949	58	51	14	7	11	16	17	5	3	3	1	9
1950	62	56	13	2	8	19	27	1	4	3	5	2
1951	51	48	16	5	5	20	18	4	2	2	8	1
1952	53	53	5	4	15	21	13	1	2	1	1	1
1953	56	50	11	8	11	21	10	3	2	3	3	5
Total	280	258	57	26	50	97	85	14	13	12	18	18

5-year survival rate treated cases 1949–1953 = 21 per cent; 1945–1953 = 21 per cent.

								10-year survivors				
1945	35	32	1	2	9	10	11	1	—	—	—	6
1946	38	34	4	7	11	8	8	2	—	—	2	5
1947	27	27	3	4	2	11	10	1	—	—	2	4
1948	55	53	7	6	10	21	16	1	3	—	3	7
Total	155	146	15	19	32	50	45	5	3	—	7	22

Analysis of treated cases—10 year

Age	Oldest 85 years, male. Treated by x-rays. Dead. Youngest 32 years, male. Treated by surgery. Alive.
Sex	Males, 112. Females, 34. Note *number of female cases.*
Biopsy	Only 88 positive biopsies recorded in 146 cases. Positive Wasserman recorded in 4 cases.

Ten-year survival rate

(1945–1948) treated cases—10 per cent.

(Five-year rate (1945–1948)—21 per cent.)

Special types of survey

Duration of symptoms

The Registrar General has asked us to enter on the new abstract cards the date of the patient's first symptom, the date when he first sought medical advice and the date when treatment began. We have found, as the result of our experience, that very often neither of these first two dates is reliable. In fact, the dates given may vary from hospital to hospital for the same patient.

Leukaemia and treatment of carcinoma of the cervix uteri by radium

A request was received in 1960 from the United States of America to find out how many cases of leukaemia have occurred, throughout the years, among patients treated with radium for carcinoma of the cervix uteri. We found only one case of leukaemia in 2,250 patients so treated.

This is the type of survey which can be carried out by the Bureau dealing as we do with a manageable unit of population.

Annual report

Since 1952, the Bureau has produced an annual report. This report has grown year by year in size and in interest. Although the basis of the report is statistical, a great effort has been made to keep the clinical findings well to the fore.

Circulation of the report

The report is not in general circulation. Copies are sent to everyone concerned in the treatment of cancer in the South Western Region, to all medical schools and colleges in Great Britain and Ireland, to the Royal Colleges, to medical schools in the Commonwealth, to other scientific and statistical organizations in the United Kingdom, to some of the Scandinavian countries, to the United States of America and to Israel. It is also sent to anyone interested in cancer who asks for it.

Content of the report

Each year we show the number of registrations by hospitals and counties. For classification we use the International Statistical Classification (I.S.C.) of the World Health Organization. In each report we publish a contribution either from a surgeon or a radiotherapist on the present position as regards treatment of cancer at some particular site or by some particular method.

The main bulk of the report is occupied by sets of tables showing the incidence of cancer at the various sites throughout the body, the method of treatment adopted and the results of treatment.

For the year 1958, we have been able to produce, for the first time, tables showing the 10-year survival rate under each site together with the 5-year survival rate for the same years (1945–1948) for comparison.

Under each site, an analysis of the cases who have survived ten years is given. This analysis deals only with treated cases. Under each site are also given tables showing the number of cases registered in the years 1949-1953 showing the 5-year survival rate.

The Tables which follow have been taken from the report in order to demonstrate their style. There are 39 such tables covering the sites of cancer throughout the body.

TABLE II

MALIGNANT GROWTHS OF TONGUE (*I.S.C.* 141)

	Total cases			*Treatment*								*Unrelated Deaths*
				All cases				*Survivors*				
	Reg'd	*Treated*	*Alive*	*Surg*	*Surg +*	*x-rays*	*Rad*	*Surg*	*Surg +*	*x-rays*	*Rad*	
								5-Year Survivors				
1949	58	51	14	7	11	16	17	5	3	3	1	9
1950	62	56	13	2	8	19	27	1	4	3	5	2
1951	51	48	16	5	'5	20	18	4	2	2	8	1
1952	53	53	5	4	15	21	13	1	2	1	1	1
1953	56	50	11	8	11	21	10	3	2	3	3	5
Total	280	258	57	26	50	97	85	14	13	12	18	18

5-year survival rate treated cases 1949–1953 = 21 per cent; 1945–1953 = 21 per cent.

								10-year survivors				
1945	35	32	1	2	9	10	11	1	—	—	—	6
1946	38	34	4	7	11	8	8	2	—	—	2	5
1947	27	27	3	4	2	11	10	1	—	—	2	4
1948	55	53	7	6	10	21	16	1	3	—	3	7
Total	155	146	15	19	32	50	45	5	3	—	7	22

Analysis of treated cases—10 year

Age . . . . { Oldest 85 years, male. Treated by x-rays. Dead. Youngest 32 years, male. Treated by surgery. Alive.

Sex . Males, 112. Females, 34. Note number of female cases.

Biopsy . . . { Only 88 positive biopsies recorded in 146 cases. Positive Wasserman recorded in 4 cases.

Ten-year survival rate

(1945–1948) treated cases—10 per cent.
(Five-year rate (1945–1948)—21 per cent.)

TABLE III

MALIGNANT GROWTHS OF STOMACH (*I.S.C.* 151)

	Total cases			*Treatment*				*Untreated*
				All cases		*Survivors*		
	Registered	*Treated*	*Alive*	*Radical surgery*	*Palliative surgery*	*Radical Surgery*	*Palliative surgery*	
						5-year		
1949	359	133	19	95	38	16	2	226
1950	409	127	18	85	42	10	4	282
1951	442	154	24	94	60	20	1	288
1952	464	180	17	106	73	13	3	284
1953	488	201	21	98	103	18	2	287
Total	2162	795	99	478	316	77	12	1367

5-year survival rate treated cases 1949–1953 = 11 per cent; 1945–1953 = 11 per cent.

						10-year		
1945	16	11	—	10	1	—	—	5
1946	97	36	4	27	9	3	—	61
1947	151	50	3	34	16	3	—	101
1948	280	104	13	63	41	10	2	176
Total	544	201	20	134	67	16	2	343

Analysis of treated cases—10 year

Age . . . . . . { Oldest 78 years, male. Partial gastrectomy. Dead.
Youngest 26 years, female. Gastrojejunostomy. Dead.

Sex . . . . . Males 123. Females, 78.

Biopsy . . . . . . Recorded as positive in only 110 cases.

Surgery . . . . . .

	All cases	*Survivors*
Total gastrectomy	26	1
Subtotal gastrectomy	12	6
Partial gastrectomy	112	9
Gastrojejunostomy	39	2
Other procedures	12	

Ten-year survival rate

(1945–1948) treated cases—8 per cent.

(Five-year rate (1945–1948)—12 per cent.)

TABLE IV

MALIGNANT GROWTHS OF COLON (EXCLUDING RECTUM) (*I.S.C.* 153)

	Total cases			*Treatment*				*Untreated*
				All cases		*Survivors*		
	Registered	*Treated*	*Alive*	*Radical surgery*	*Palliative surgery*	*Radical surgery*	*Palliative surgery*	
						5-year		
1949	315	205	47	122	83	46	—	110
1950	373	248	69	158	90	65	4	125
1951	369	222	76	155	67	69	7	147
1952	363	231	62	155	76	56	6	132
1953	424	249	61	152	97	55	5	175
Total	1844	1155	315	742	413	291	22	689

5-year survival rate treated cases 1949–1953 = 27 per cent; 1945–1953 = 28 per cent.

						10-year		
1945	27	17	6	11	6	5	1	10
1946	99	54	13	39	15	12	1	45
1947	121	78	23	63	15	22	1	43
1948	185	122	26	65	57	26	—	63
Total	432	271	68	178	93	65	3	161

Analysis of treated cases—10 year

Age	Oldest 84 years, female. No biopsy. Colostomy only. Dead. Youngest 21 years, female. Positive biopsy. ?operation—treated by surgery. Dead.		
Sex	Males, 121. Females, 150.		
Biopsy	Recorded as positive in only 126 cases.		
			Survivors
Surgery	Resection	104	34
	Hemicolectomy	43	11
	Paul-Mikulicz	33	12
	Colostomy	49	9
	Anastomosis only	27	1
	Other procedures	15	1

Site	Pelvic colon 111	Hepatic flexure 9		
	Caecum 37	Ascending colon 17		
	Transverse colon 41	Descending colon 19		
	Splenic flexure 24	Not stated 13		

Ten-year survival rate
(1945–1948) treated cases—25 per cent.
(Five-year rate (1945–1948)—32 per cent.)

TABLE V

MALIGNANT GROWTHS OF THORACIC ORGANS (*I.S.C.* 162-5)

	Total cases			*Treatment*						*Not treated*
				All cases			*Survivors*			
	Reg'd	*Treated*	*Alive*	*Surg*	*Surg+*	*Rad*	*Surg*	*Surg+*	*Rad*	
							5-year			
1949	310	159	15	20	11	128	9	2	2	151
1950	399	201	7	11	9	181	2	1	4	198
1951	485	230	9	39	9	182	6	1	2	255
1952	522	241	17	44	15	181	12	2	3	281
1953	567	282	17	56	15	211	12	—	4	285
Total	2283	1113	65	170	59	883	41	6	15	1170

5-year survival rate treated cases 1949–1953 = 5 per cent; 1945–1953 = 5 per cent.

							10-year			
1945	37	28	—	—	—	28	—	—	—	9
1946	135	57	3	9	3	45	2	—	1	78
1947	171	75	3	15	4	56	3	—	—	96
1948	229	123	2	16	14	93	1	—	1	106
Total	572	283	8	40	21	222	6	—	2	289

Analysis of treated cases—10 year

Age . . . . . Oldest 76 years, female. No biopsy. Treated by x-rays. Dead.
Youngest 30 years, male. Positive biopsy. Treated by surgery + x-rays. Dead.

Sex . . . . . . Males, 253. Females, 30.

Biopsy . . . . . . Recorded as positive in 164 cases.

		All cases	*Survivors*
Surgery	Pneumonectomy	37	6
	Lobectomy	5	—
	Other procedures	19	—

Ten-year survival rate
(1945–1948) treated cases—2 per cent.
(Five year rate (1945–1948)—4 per cent.)

TABLE VI

MALIGNANT GROWTHS OF BREAST (*I.S.C.* 170)

STAGE I

(We use the Manchester staging)

	Total cases			*Treatment*					
				All cases			*Survivors*		
	Reg'd	*Treated*	*Alive*	*Surg*	*Surg+*	*Rad*	*Surg*	*Surg+*	*Rad*
								5-year	
1949	344	333	197	62	234	37	41	144	12
1950	319	317	222	79	219	18	55	155	10
1951	330	326	237	96	218	10	74	160	3
1952	335	334	226	81	248	5	52	172	2
1953	355	348	212	80	258	8	53	156	3
Total	1683	1658	1094	398	1177	78	275	787	30

5-year survival rate treated cases 1949–1953 = 65 per cent; 1945–1953 = 65 per cent.

								10-year	
1945	136	136	59	16	109	11	6	50	3
1946	192	192	76	23	162	7	15	57	4
1947	178	178	72	14	150	14	6	62	4
1948	278	277	110	27	230	20	11	96	3
Total	784	783	317	80	651	52	38	265	14

Analysis of treated cases—10 year

Age . . . . . . Oldest 86 years. Sarcoma. Treated with surgery + x-rays. Dead.
or 85 years. Treated with surgery + x-rays. Alive.
Youngest 22 years. Duct carcinoma. Treated by surgery +x-rays. Alive.

Sex . . . . . . One male.

Biopsy . . . . . . Recorded as positive in 382 cases only.

Surgery . . . . . . 104 simple mastectomies. Remainder radical.

Pathology . . . . . .
Paget's disease 20
Duct carcinoma 10
Sarcoma 4
Remainder spheroidal-celled adenocarcinoma.
One case bilateral carcinoma. Dead.

Ten-year survival rate

(1945–1948) treated cases—40 per cent.

(Five-year rate (1945–1948)—63 per cent.)

TABLE VII

MALIGNANT GROWTHS OF UTERUS (*I.S.C.* 172-4)

EARLY

	Total cases		*Treatment*					
			All cases			*Survivors*		
	Registered	*Alive*	*Surg*	*Surg+*	*Rad*	*Surg*	*Surg+*	*Rad*
						5-year		
1949	99	65	45	42	10	32	30	3
1950	115	85	54	53	8	43	36	6
1951	104	84	59	35	8	48	31	5
1952	135	92	75	47	13	51	33	8
1953	113	71	68	35	8	41	24	6
Total	566	397	301	212	47	215	154	28

5-year survival rate treated cases 1948–1953 = 70 per cent; 1945–1953 = 69 per cent.

						10-year		
1945	18	10	2	12	3	2	7	1
1946	38	19	6	25	6	4	13	2
1947	31	9	8	18	5	2	7	—
1948	64	24	27	28	8	13	10	1
Total	151	62	43	83	22	21	37	4

Analysis of treated cases—10 year

Age . . . .
- Oldest 80 years. Treated by x-rays. Positive biopsy. Dead.
- Youngest 30 years. Treated by surgery + x-rays. Positive biopsy. Alive.

Biopsy . . . . . .
- *Recorded as positive in 126 cases.*
- Three cases of sarcoma.
- One case diagnosed histologically as chorionepithelioma. Age 31 years. Treated by surgery + x-rays. Alive.

Ten-year survival rate

(1945–1948) treated cases—41 per cent.

(Five-year rate (1945–1948)—62 per cent.)

TABLE VIII

MALIGNANT MELANOMA (*I.S.C.* 190)

	Total cases		*Survivors*
	Registered	*Treated*	*5-year*
1949	45	43	24
1950	33	33	15
1951	29	27	10
1952	33	30	12
1953	39	35	15
Total	179	168	76

5-year survival rate treated cases 1949–1953 = 45 per cent; 1945–1953 = 45 per cent.

			10-year
1945	8	5	3
1946	13	8	4
1947	18	17	4
1948	41	38	12
Total	80	68	23

Analysis of treated cases—10 year

Age . . . . Oldest 88 years, male. Positive biopsy. Face. Treated by surgery + x-rays. Dead.
Youngest 21 years, male. Positive biopsy. Neck. Treated by surgery. Alive.

Sex . . . . Males, 30. Females, 38.

Biopsy . . . . Recorded as positive in all but one case.

Ten-year survival rate
(1945–1948) treated cases—33 per cent.
(Five-year rate (1945–1948)—45 per cent.)

Commentary on the Incidence Table (1957).

The Incidence Table (IX) shows clearly the incidence of cancer per 100,000 of the population in the various sites throughout the body. It also shows the incidence in males and females and the total rate per 100,000. Amongst other things, it enables one to compare the incidence from year to year.

It is to be noted that in 1957 the number of cases of carcinoma of the stomach is 948—seven more than in 1956. Carcinoma of the large intestine (excluding rectum) shows 817 cases as against 758 in 1956. Carcinoma of the trachea, bronchus and lung shows 1,130 cases as against 1,017, an increase of 113. The huge preponderance of males with cancer of the lung is maintained—950 males and 180 females.

Carcinoma of the breast shows 1,204 cases in 1957 as against 1,070 in 1956. Only 10 of these cases occurred in males.

TABLE IX

South Western Region Cancer Incidence 1957

(Rate per 100,000 of population)

Male—1,364,000: *Female*—1,441,000

I.S.C. No	*Site*	*Male*	*Rate per 100,000*	*Female*	*Rate per 100,000*	*Total rate per 100,000*
140–148	**Buccal cavity and pharynx**	205	15·0	116	8·1	11·4
140	Lip	68	5·0	9	0·6	2·8
141	Tongue	36	2·7	18	1·3	1·9
142	Salivary glands	26	1·9	34	2·4	2·1
143	Floor of mouth	12	0·9	7	0·5	0·7
144	Mouth other parts	17	1·2	12	0·8	1·0
145	Oral mesopharynx	17	1·2	5	0·4	0·8
146	Nasopharynx	4	0·3	—	—	0·1
147	Hypopharynx	18	1·3	25	1·7	1·5
148	Pharynx	7	0·5	6	0·4	0·5
150–159	**Digestive organs**	1435	105·2	1503	104·3	104·8
150	Oesophagus	93	6·8	98	6·8	6·8
151	Stomach	532	39·0	416	28·9	33·8
152	Small intestine	14	1·0	18	1·2	1·2
153	Large intestine (except rectum)	303	22·2	514	35·7	29·1
154	Rectum	290	21·3	222	15·4	18·3
155 & 156	Biliary passages and liver	81	5·9	90	6·3	6·1
157	Pancreas	114	8·4	117	8·1	8·2
158	Peritoneum	5	0·4	26	1·8	1·1
159	Digestive unspecified	3	0·2	2	0·1	0·2
160–165	**Respiratory system**	1045	76·6	215	14·9	44·9
160	Nose and nasal cavities	20	1·5	13	0·9	1·2
161	Larynx	65	4·8	15	1·0	2·8
162 & 163	Trachea, bronchus and lung	950	69·6	180	12·5	40·3
164	Mediastinum	8	0·6	7	0·5	0·5
165	Thoracic organs (secondary)	2	0·1	—	—	0·1
170–181	**Breast and genito-urinary**	781	57·3	2228	154·6	107·3
170	Breast	10	0·7	1194	82·9	42·9
171	Cervix uteri	—	—	285	19·8	10·2
172	Corpus uteri	—	—	227	15·7	8·1
173 & 174	Uterus other and unspecified	—	—	41	2·8	1·5
175	Ovary	—	—	294	20·4	10·5
176	Female genital	—	—	53	3·7	1·9
177	Prostate	443	32·5	—	—	15·8
178	Testis	40	3·0	—	—	1·4
179	Male genital	24	1·8	—	—	0·8
180	Kidney	59	4·3	33	2·3	3·3
181	Bladder	205	15·0	101	7·0	10·9
190–199	**Other and unspecified sites**	792	58·1	757	52·5	55·2
190	Malignant melanoma	32	2·3	46	3·2	2·8
191	Other skin, including rodent ulcer	515	37·8	438	30·4	34·0
192	Eye	7	0·5	7	0·5	0·5
193	Brain and central nervous system	95	7·0	86	6·0	6·5
194	Thyroid	21	1·5	33	2·3	1·9
195	Other endocrine	9	0·7	8	0·5	0·6
196	Bone	23	1·7	14	1·0	1·3
197	Connective tissue	21	1·5	31	2·1	1·8
198	Lymph nodes	17	1·3	10	0·7	1·0
199	Other and unspecified	52	3·8	84	5·8	4·8
200–205	**Lymphatic and haematopoietic tissue**	213	15·6	169	11·7	13·6
200	Lymphosarcoma and reticulosarcoma	55	4·0	39	2·7	3·4
201	Hodgkin's disease	25	1·8	20	1·4	1·6
202	Other forms of lymphoma (reticulosis)	14	1·0	6	0·4	0·7
203	Multiple myeloma (plasmocytoma)	30	2·2	22	1·5	1·8
204	Leukaemia and aleukaemia	88	6·5	82	5·7	6·1
205	Mycosis fungoides	1	0·1	—	—	—
		4471	327·8	4988	346·1	337·2

In the following two tables, Table X is designed to show at which sites throughout the body cancer is recorded to have occurred during the years 1945–1953 in order of frequency, and Table XI shows the chances of survival after treatment during the same years.

If these two tables are considered together some interesting facts emerge. For instance, it will be noticed that while malignant growths of the breast are first in frequency, they are twenty-fifth on the virulence table; whereas malignant growths of thoracic organs are second in frequency and almost at the top of the virulence table.

TABLE X

SUMMARY OF INCIDENCE RATE IN ORDER OF HIGHEST RATE 1945–1953

Priority	*Site*	*Total cases*	*Alive*	*5-yr. survival rate in all cases (Per cent)*	*5-yr. survival rate treated cases (Per cent)*
1	Breast	5980	2525	42	43
2	Thoracic	2855	79	2·7	5
3	Stomach	2706	126	4·6	11
4	Colon	2276	403	17	27
5	Rectum	2108	365	17	25
6	Cervix	1443	482	33	35
7	Prostate	1197	191	16	18
8	Uterus	1079	543	50	56
9	Ovary	1039	190	18	26
10	Bladder	914	220	24	28
11	Oesophagus	762	13	1·7	2
12	Lip	649	389	60	60
13	Brain and central nervous system	551	79	14	30
14	Pancreas	527	8	1·5	4
15	Leukaemia	519	46	8·9	15
16	Mouth	464	96	20	21
17	Tongue	435	90	20	21
18	Larynx	418	90	21	23
19	Lymphadenoma and reticulosis	412	99	24	27
20	Female genital organs	411	155	37	41
21	Kidney	325	61	18	26
22	Lymphosarcoma and reticulosarcoma	300	66	22	24
23	Bone	293	56	19	22
24	Malignant melanoma	265	107	40	45
25	Hypopharynx	223	13	5 8	6
26	Salivary glands	211	133	63	65
27	Thyroid	207	60	28	33
28	Testis	203	109	48	55
29	Nasopharynx	200	29	14	15
30	Male genital organs	177	85	48	50
31	Nose and nasal sinuses	176	38	21	22
32	Eye	62	43	69	74

This table is designed to show at which sites cancer is recorded as having occurred during the years 1945–1953 in order of frequency. It also shows the five-year survival rate for all cases and for treated cases during the same years.

TABLE XI

SUMMARY OF VIRULENCE RATE IN ORDER OF MORTALITY 1945–1953

Priority	*Site*	*5-yr. survival rate treated cases (Per cent)*	*Cases registered*	*Alive*
1	Oesophagus	2	762	13
2	Pancreas	4	527	8
3	Thoracic	5	2855	79
4	Hypopharynx	6	223	13
5	Stomach	11	2706	126
6	Leukaemia	15	519	46
7	Nasopharynx	15	200	29
8	Prostate	18	1197	191
9	Tongue	21	435	90
10	Mouth	21	464	96
11	Bone	22	293	56
12	Nose and nasal sinuses	22	176	38
13	Larynx	23	418	90
14	Lymphosarcoma and reticulosarcoma	24	300	66
15	Rectum	25	2108	365
16	Kidney	26	325	61
17	Ovary	26	1039	190
18	Lymphadenoma and reticulosis	27	412	99
19	Colon	28	2276	403
20	Bladder	28	914	220
21	Brain and central nervous system	30	551	79
22	Thyroid	33	207	60
23	Cervix	35	1443	482
24	Female genital organs	41	411	155
25	Breast	43	5980	2525
26	Malignant melanoma	45	265	107
27	Male genital organs	50	177	85
28	Testis	55	203	109
29	Uterus	56	1079	543
30	Lip	60	649	389
31	Salivary glands	65	211	133
32	Eye	74	62	43

This table shows the chance of survival under each site for the years 1945–1953. It gives the five-year survival rate for treated cases.

OTHER CENTRES IN ENGLAND AND WALES

Having dealt in detail with the organization of one cancer registration bureau —the South Western—we now turn to the present position as regards other centres in England and Wales. (This information is given by an official of the Ministry of Health.)

There are now 15 regions. Nine regions have functioning centres of their own and three (the South East Metropolitan, South West Metropolitan and Wessex) are incorporated into the Royal Marsden Scheme.

Wales has made a start. The North West Metropolitan has a pilot scheme and contemplates expansion. Manchester has no plans. It can be said that progress is being made in the Leeds, Sheffield and East Anglia regions. The methods of

organizing the bureaux and the scope of each varies considerably in each region. In only two regions (the South Western and the East Anglian) have medical men been specially appointed to direct the organization although the North West Metropolitan has a surgeon at the head. Only one region (the South Western) can be said to have a fully functioning bureau providing all the services which a bureau can provide. Nevertheless, England and Wales now register and follow-up a greater number of cases in a whole population than any other country.

Table XII gives the latest figures from the General Register Office (columns 1, 2 and 3). Columns 4 and 5 have been added by a medical statistician at the Ministry of Health. No figures are included for Scotland or Northern Ireland. The former has a scheme comparable to ours in the South Western Region. The Northern Ireland scheme is in its infancy.

Manchester has been shown as nil in the 1958 column as the Christie Hospital has withdrawn from the scheme.

TABLE XII

CANCER REGISTRATION — ENGLAND AND WALES

Region	*Not including registrations from death certificates average 10–15 per cent of total*		*Population (thousands)*	*Expected total number*	
	1957	1958		*Estimated at 2·5 per* 1000	*Estimated at 3 per* 1000
Newcastle	6348	6848	2971	7430	8910
Leeds	6830	6855	3075	7690	9220
Sheffield	6952	8037	4286	10700	12840
East Anglia	2946	4300	1506	3750	4500
N.W. Metropolitan	7192	8071	4001	10000	12000
N.E. Metropolitan	6958	7318	3144	7850	9420
S.E. Metropolitan	4547		3240	8100	9720
		16378		20100	24120
S.W. Metropolitan	7369		4789	12000	14400
Oxford	4230	4200	1536	3750	4500
South Western	7557	7550	2807	7000	8400
Wales	1353	1341	2040	5100	6120
Birmingham	8655	8700	4605	11500	13800
Manchester	3814	Nil	4383	11000	13200
Liverpool	7510	7422	3776	6940	8330
Wessex	Figures included in S.W. Metropolitan				
Total	82261	90820	45,159,000	112910	135330

Total deaths from malignant disease 1958 = 95069.

REPORTS

Reports have been issued by the Royal Marsden Hospital, Birmingham Group of Hospitals (their reports deal with cancer at one or two sites of the body in each volume), Liverpool centre, East Anglian centre, and the South Western Bureau.

TABLE XI

SUMMARY OF VIRULENCE RATE IN ORDER OF MORTALITY 1945–1953

Priority	*Site*	*5-yr. survival rate treated cases (Per cent)*	*Cases registered*	*Alive*
1	Oesophagus	2	762	13
2	Pancreas	4	527	8
3	Thoracic	5	2855	79
4	Hypopharynx	6	223	13
5	Stomach	11	2706	126
6	Leukaemia	15	519	46
7	Nasopharynx	15	200	29
8	Prostate	18	1197	191
9	Tongue	21	435	90
10	Mouth	21	464	96
11	Bone	22	293	56
12	Nose and nasal sinuses	22	176	38
13	Larynx	23	418	90
14	Lymphosarcoma and reticulosarcoma	24	300	66
15	Rectum	25	2108	365
16	Kidney	26	325	61
17	Ovary	26	1039	190
18	Lymphadenoma and reticulosis	27	412	99
19	Colon	28	2276	403
20	Bladder	28	914	220
21	Brain and central nervous system	30	551	79
22	Thyroid	33	207	60
23	Cervix	35	1443	482
24	Female genital organs	41	411	155
25	Breast	43	5980	2525
26	Malignant melanoma	45	265	107
27	Male genital organs	50	177	85
28	Testis	55	203	109
29	Uterus	56	1079	543
30	Lip	60	649	389
31	Salivary glands	65	211	133
32	Eye	74	62	43

This table shows the chance of survival under each site for the years 1945–1953. It gives the five-year survival rate for treated cases.

OTHER CENTRES IN ENGLAND AND WALES

Having dealt in detail with the organization of one cancer registration bureau —the South Western—we now turn to the present position as regards other centres in England and Wales. (*This information is given by an official of the Ministry of Health.*)

There are now 15 regions. Nine regions have functioning centres of their own and three (the South East Metropolitan, South West Metropolitan and Wessex) are incorporated into the Royal Marsden Scheme.

Wales has made a start. The North West Metropolitan has a pilot scheme and contemplates expansion. Manchester has no plans. It can be said that progress is being made in the Leeds, Sheffield and East Anglia regions. The methods of

Where possible, it would be better to appoint a medical man as head of the bureau: this is a very suitable job for a retired surgeon.

What is the use of cancer registration to the clinicians?

This question is often asked and the answer would appear to be that the ultimate value of registration will only be obvious when most of the centres are able to produce reports which indicate clearly and concisely what are the results of the various methods of treatment of cancer.

This is what has been aimed at in the reports of the South Western Regional Cancer Records Bureau.

ACKNOWLEDGEMENTS

The author wishes to acknowledge his indebtedness to Dr. A. Cruickshank, medical statistician to the Ministry of Health and to Dr. A. McKenzie, medical statistician to the General Register Office.

REFERENCES

General Register Office (1952). *Cancer Registration in England and Wales.* Supplement. General Register Office Studies on Medical and Population Subjects. London; H.M. Stationery Office.

Register General's Statistical Review of England and Wales (1949). General Morbidity, Cancer and Mental Health. London; H.M. Stationery Office.

— (1950–51). *Ibid.*

Stocks, P. (1950). *Cancer Registration in England and Wales.* General Register Office Studies on Medical and Population Subjects No. 3. London; H.M. Stationery Office.

Vick, R. M. (1955). " Progress in Cancer Registration: a Survey of the Development of a Cancer Records Bureau from 1945 to 1954." *Brit. med. J.*, 1, 660.

— (1958). " Progress in Cancer Registration: a Survey of the Further Development of a Cancer Records Bureau from 1954 to 1956." *Ibid.*, 1, 1406.

Many of the teaching hospitals produce cancer statistics in connexion with their other statistical returns. University College Hospital has produced a report, dealing with all the cancer patients in the hospital, covering a period of years and the results of treatment.

These reports are not in general circulation but, presumably, can be obtained by application to the centres or hospitals concerned.

Cancer registration on a National basis

At intervals, figures are published by the General Register Office—sometimes through the Ministry of Health.

These figures give the results obtained by study of the vast returns gradually accumulating at the General Register Office and, at intervals, a clinical assessment is made.

Cancer registration on a local basis

This has been dealt with by reference to experiences in working at one Regional Hospital Bureau.

Reports from this Bureau have been issued year by year from 1952 to 1958 and they have always had a clinical bias. The results of treatment have been emphasized by the use of a series of statistical tables.

CONCLUSIONS

National registration

It may be said that National registration only really began after the war with the establishment of the National Health Service.

The statistical records are all gathered together by the General Register Office, which publishes figures and draws conclusions from them at intervals. Some of these reports are included in the Annual Report of the Chief Officer of the Ministry of Health.

The records of cancer cases are sent to the General Register Office on abstract cards from the various regional centres and the follow-up of patients is also undertaken by the centres and the details transmitted to the General Register Office at stated intervals. In one or two areas, this is still carried out direct by the hospitals, where a cancer records centre is not established.

Regional centres

Details of these centres and their work are contained in this article. The establishment of the centres has been left to each Regional Hospital Board and the result has been a considerable variation in each region.

It is obvious that cancer registration, as a whole, will not be satisfactory until efficient centres are set up throughout the country—all of which will not only record cases with the General Register Office but also, ideally, produce reports of their own. It would be wise for these regional centre reports to be kept as simple as possible, with a very definite clinical basis.

Their reports should be widely circulated amongst general practitioners and, of course, sent to all those people dealing with the treatment of cancer.

Argentaffin cells show a typical granular appearance, the significance of which has puzzled histologists since Kultschitzky (1897) demonstrated their acidophilic nature. Barter and Pearse (1955) have found that the typical fluorescence and histochemical reactions of the granules were due to a chemical artefact produced by the interaction of formalin and 5-HT. Their finding would explain the failure to demonstrate the granules in unfixed material and after using fixatives not containing formalin.

Metabolic pathway

5-Hydroxytryptamine is formed from the essential aminoacid tryptophan. This is hydroxylated to 5-hydroxytryptophan, which is then decarboxylated to 5-HT (Fig. 14). Hydroxylation reactions take place usually completely in the liver, but in this particular instance it has been suggested that the entire synthesis occurs in the argentaffin cell. Recently, however, it has been shown that the decarboxylase is present in high concentrations in the kidney, liver, stomach and in certain areas in the brain. The argentaffin cell may synthesize only 5-hydroxytryptophan with the decarboxylation occurring in the other sites. This mode of synthesis would explain the presence of 5-HT in the brain, for it is known that it cannot cross the blood-brain barrier whereas the precursor, 5-hydroxytryptophan, is able to reach the central nervous system. In the brain there are areas containing 5-hydroxytryptophan decarboxylase where the cycle could be completed.

The deamination of 5-HT to 5-hydroxyindole acetic acid (5-HIAA) is catalysed by mono-amine oxidase. This enzyme is present in the lungs, liver and the hypothalamic region of the brain.

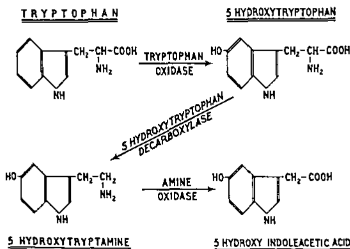


FIG. 14.—Metabolic pathway of 5-hydroxytryptamine.

Functions

Clearly 5-HT must play a most important part in the endocrine balance of the body. Many suggestions have been made about these possible functions but, as yet, the true physiological function is unknown. It is possible to give only the briefest

CARCINOID TUMOURS

By A. J. DAVIES, M.S., F.R.C.S.

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Until the last few years carcinoid tumours have been treated as pathological curiosities. Since 1954, when Thorson and his colleagues correlated the syndrome of carcinoidosis, cutaneous flushing and valvular lesions of the heart, they have become of great interest clinically, pathologically and biochemically. For many years physiologists and biochemists have been investigating a substance, 5-hydroxytryptamine, that Lembeck (1953) demonstrated in large quantities in carcinoid tumours. Literally hundreds of papers can be found in the literature dealing with every aspect of the problem. The intensive studies of the physiology and pharmacology of 5-hydroxytryptamine have undoubtedly been stimulated by this unusual syndrome.

5-HYDROXYTRYPTAMINE

There has been some confusion over the nomenclature in the past. The American workers prefer to use the term "serotonin" whereas many other workers adhere to the terminology suggested by Erspamer that it should be named "enteramine". In Great Britain the chemical name is usually preferred—5-hydroxytryptamine (or 5-HT for brevity).

History

For nearly a hundred years it has been recognized that vasoconstrictor substances were found in clotted blood, but only recently has the identity of this substance been established. Rapport, Green and Page (1948) were able to isolate it from the serum, identifying it as 5-hydroxytryptamine (5-HT). Hamlin and Fischer (1951) synthesized this 5-hydroxyindole and confirmed that it was identical with the serum vasoconstrictor.

Vialli and Erspamer (1937) obtained a substance, after extraction of the rabbit gastro-intestinal mucosa, whose origin they attributed to the enterochromaffin or argentaffin cells; they named it "enteramine". Erspamer and Asero (1952) showed that it was identical with 5-HT.

Distribution

5-Hydroxytryptamine occurs in both the plant and animal kingdoms. In vertebrates it can be extracted from the gastro-intestinal tract, spleen and brain. Larger quantities are found in the terminal ileum and appendix. It is in these sites that large numbers of argentaffin cells are present.

Physiological levels

The 5-HT content of blood is small, the levels are 0·16 microgram per millilitre in whole blood and 0·07 microgram per millilitre in serum (Snow and his colleagues, 1955). Small quantities, 60–160 micrograms per 24 hours, are excreted in the urine. 5-HIAA is normally excreted in the urine at levels of 2–10 milligrams per 24 hours, but there is considerable daily and individual variation.

Pathological variations

Decreased levels

Pare, Sandler and Stacey (1958) demonstrated a decrease in the level of 5-HT in the blood of patients suffering from phenylketonuria. They suggested that this decrease was caused by circulating aromatic acids inhibiting or depressing some part of the tryptophan pathway, possibly the 5-hydroxytryptophan decarboxylase.

Bigelow (1953) reported that he found low 5-HT levels, measured as platelet-derived serum vasoconstrictor, in patients with thrombocytopenia, haemophilia, purpura and hypoprothrombinaemia. The levels in the patients with thrombocytopenia were corrected after splenectomy.

Increased levels

In many patients with malignant carcinoid tumours there is a marked increase in the 5-HT serum levels. Pernow (1958) reported values for the serum of 0·25–6·5 micrograms per millilitre (normal 0·07 micrograms per millilitre). There is also an increased excretion of 5-HT in the urine—0·10–20 micrograms per millilitre (normal 0·01–0·02 micrograms per millilitre). Smith and his colleagues (1957) reported a patient with a renal metastasis who excreted 40 milligrams of 5-HT in 24 hours. 5-HIAA excretion is also increased, 20–900 milligrams in 24 hours having been recorded (normal 2–10 milligrams per 24 hours). There is no measurable amount of 5-HIAA in the serum of normal subjects or carcinoid patients.

Boyland, Gasson and Williams (1956) found that patients suffering from carcinoma of the larynx and bronchus had an increased excretion of 5-HT and 5-HIAA after feeding with 2 grammes of *l*-tryptophan. This increase did not occur with normal subjects or patients suffering from diseases other than cancer, nor was it as large as the excretion levels recorded in patients with carcinoid tumours.

CARCINOID TUMOURS

History

The name "carcinoid" was suggested by Obendorfer in 1907. He wished to separate a group of tumours, that he believed to be benign, and which were histologically unlike the adenocarcinomas of the bowel. Lubarsch (1888) gave the earliest lucid case records of tumours that, from the description, must have been carcinoids. He considered them to be benign and described them as atypical primary carcinomas of the bowel. In 1890 Ransom described an ileal tumour which, from its gross appearance, must have been a carcinoid with widespread hepatic deposits.

After Obendorfer's suggested nomenclature had been adopted there was considerable disagreement about the tumour's developmental origin. Amongst the many suggestions were that they were related to the basal-celled carcinomas

outline of the subject for there have been a vast number of investigations reported (Page, 1958).

Haemostasis

For almost a hundred years it has been recognized that vasoconstrictor substances were liberated when blood clots. Platelets transport 5-HT and it has been suggested that they liberate it on breakdown giving rise to local vasoconstriction. It seems unlikely, however, that sufficient 5-HT would be liberated at the site of the blood clot to contract the damaged vessels.

An alternative suggestion (Milne and Cohn, 1957) is that 5-HT inhibits the factor that is present in circulating blood to prevent spontaneous clot formation. Haverback and his colleagues (1957) have shown that reduction of platelet 5-HT by reserpine feeding produces no alternation of the bleeding or clotting time such as one would have expected if haemostasis was the prime function.

Maintenance of arteriolar tone

Page and McCubbin (1953) suggested that the physiological function of 5-HT was to maintain the arteriolar tone and so control the blood pressure. They believed that its action was not directly on the arteriolar smooth muscle but reflexly by neurogenic inhibition. The majority of workers do not agree with this theory. The effect varies considerably for hypotensive, normotensive and hypertensive responses can be obtained. Erspamer (1954) pointed out that to produce even minor blood pressure changes in man 60–120 micrograms of 5-HT intravenously was required—the amount contained in 1200–2400 millilitres of blood.

Control of the kidney circulation

It is known that 5-HT has a powerful antidiuretic effect. Erspamer (1954) believed that it controlled the circulation of the kidney and so the excretion of urine. There is, however, considerable species variation, and it is far from clear whether it has this physiological effect in man.

Maintenance of normal mental processes

5-Hydroxytryptamine is necessary for the normal functioning of the brain. This has been demonstrated by the production of a variety of temporary mental disorders in normal subjects after administering 5-HT antimetabolites, such as mescaline. The suggested mode of action is that it is the synaptic mediator of the central parasympathetic, much as noradrenaline performs the same function in the sympathetic nervous system. Woolley and Shaw (1954) believed that alteration in the level of 5-HT in the brain was the cause of mental disease and suggested that schizophrenia was associated with a low level.

Maintenance of normal intestinal peristalsis

Bulbring and Lin (1958) believed that 5-HT is concerned with the maintenance of normal peristalsis. They suggested that the 5-HT after synthesis by the argentaffin cells was stored locally and only released when there was a rise in intraluminal pressure. Its action was possibly to sensitize the presso-receptors in the bowel wall.

TABLE I

THE DISTRIBUTION OF TUMOURS IN THE GASTRO-INTESTINAL TRACT

Organ	*Benign*	*Malignant*
Stomach	28	12
Duodenum	18	6
Gall bladder	3	1
Jejunum	14	14
Ileum	101	133
Meckel's diverticulum	11	2
Appendix	233	22
Ileo-caecal valve and colon	11	33
Rectum	79	18
Flushing syndrome	—	42
Unknown primary	—	3
Ovarian teratoma	7	—

(Table II). There are, however, two notable exceptions to this. First, the appendicular carcinoids occur in a younger age group, 28·8 and 26·2 years for benign and malignant lesions respectively. The reason for this may be explained in three ways.

(1) These tumours are slowly growing but nevertheless will obstruct the appendicular lumen earlier than ileal lesions will cause small gut obstruction.

(2) This is the age group in which acute appendicitis is commonest and the tumour is found incidentally.

(3) The appendix is removed more often than any other organ for vague abdominal pain which could have been caused by the tumour or by some unrelated cause, or is removed as an incidental procedure at some other abdominal operation.

TABLE II

AGE DISTRIBUTION OF PATIENTS WITH TUMOURS

Organ	*Benign (years)*	*Malignant (years)*
Stomach	60·7	53·5
Duodenum	56·2	55·4
Gall bladder	65	68
Jejunum	53·7	65·2
Ileum	62·5	56·5
Meckel's diverticulum	53·4	54
Appendix	28·8	26·2
Ileo-caecal valve and colon	61·6	54·1
Rectum	50·6	39
Flushing syndrome	—	48·1

Secondly, the rectal carcinoid tumours, particularly the malignant cases, also have a significantly lower age group (39 years). This could be explained by the fact that at this age patients suffering from rectal bleeding from some unrelated cause are submitted to a routine sigmoidoscopic examination to exclude carcinoma. The carcinoid is found coincidentally. The truth of this is confirmed by the fact that of 79 benign cases described in the literature 62 were found incidentally on sigmoidoscopy.

of skin (Bunting, 1904), that they arose from pancreatic rests (Trappe, 1907), submucous rests (Toennissen, 1909), epithelial rests (Engel, 1923), Auerbach's plexus (Ehrlich, 1912), sympathetic nervous system (Lewis and Geschickter, 1934), and that they were tissue malformations or a dysontogenesis like the hamartoma (Semsroth, 1928). It is now generally accepted that they develop from argentaffin cells.

The majority of workers used the term *carcinoid* to describe these tumours. Dockerty and Ashburn (1943) criticized the use of this name because it did not stress the malignant or potentially malignant nature of the lesion. They preferred to classify the tumour as adenocarcinoma Grade I (carcinoid). There has recently been a tendency to use the term argentaffin carcinoma or more commonly argentaffinoma. This has, however, lead to some confusion, for sometimes a tumour, that is typical histologically and biochemically, will not show silver reduction. Even more striking is the presence of argentaffin and non-argentaffin staining areas in the same tumour. Pearse (1953) believed that the more selective histochemical tests, such as Gibbs' reaction, give positive results where the silver reactions are absent. For this reason many workers prefer to use the old name *carcinoid*, or *carcinoidosis* when the condition is widespread.

In the first fifty years of this century, apart from several excellent review articles (Forbus, 1925; Wyatt, 1938, Grimes and Bell, 1949), little of importance was added to our knowledge of carcinoids. Interest was reawakened when Thorson and his colleagues (1954) described a newly recognized syndrome of carcinoidosis, vascular cutaneous flushing, valvular lesions of the heart, and hyperactivity of the bowel. There have been several descriptions of the condition in the few years to prior this report, but the authors had failed to correlate the clinical and pathological findings (Millman, 1943; Biorck, Aken and Thorson, 1952; Isler and Hedinger, 1953).

The earliest case descriptions of the carcinoid syndrome were given by Sir Maurice Cassidy in 1931 and 1933, at the Royal Society of Medicine. He presented two patients with "carcinomatosis" exhibiting curious flushing attacks and from his description of these attacks there is little doubt that they in fact had carcinoid tumours. One of them was found to have a pulmonary stenosis at subsequent necropsy. Cassidy believed that these vascular phenomena were due to malignant replacement of the adrenal glands. At subsequent post-mortem study in neither case were the glands shown to have been involved.

PATHOLOGY

Distribution of tumours

Carcinoid tumours are found throughout the gastro-intestinal tract. The largest number of them have been described in the ileum, usually within two feet of the ileo-caecal valve and in the appendix (Table I). These are the areas of greatest concentration of the argentaffin cells. The ovarian teratomas have been included in this group for, in the majority of instances, the tumour developed in intestinal epithelium rather than respiratory remnants.

Age incidence

The age incidence for the whole group of tumours is much like that for other types of cancer, the middle and older age groups being more commonly affected

action of the large quantities of 5-HT produced locally by the tumour. Raiford (1933) did not believe that this is only a muscle hypertrophy, but that there is a marked connective tissue hyperplasia producing an abnormally dense stroma.

Histological appearance

The submucous appearance of the tumour is seen (Fig. 15). In some of the larger lesions there may be many microscopic areas of surface ulceration. The masses of tumour tissue often undergo a central necrosis or liquefaction, an appearance more commonly seen in hepatic metastases. Typically, the groups of cells may be



Fig. 15.—Carcinoid tumour of the appendix. The submucous position is demonstrated and also the peripheral palisading of darkly-staining cells. (Haematoxylin and eosin. ×100.)

arranged in columns, or islands, or they may attempt to form tubules or acini. Around the periphery of these tumour clumps there is often a palisading of darkly staining granular argentaffin cells. In the centre of the mass there are poorly staining grey round cells.

Between the clumps of tumour cells there is a variable amount of fibrous tissue stroma. Usually the stroma is marked, isolating the clumps of cells, but occasionally the stroma is absent and there is a solid sheet of malignant cells (Figs. 16 and 17). The amount of stroma does not seem to be related to the degree of malignancy of the tumour.

The spread is by infiltration through the tissue planes. Carcinoids appear to favour spread via the perineural lymphatics, but finally the large lymph trunks, glands and blood vessels are invaded.

Sex incidence

For the whole series the sex distribution for both benign and malignant lesions is approximately equal (Table III). If, however, only the appendicular lesions are considered it will be seen that there is a marked female predominance (168 to 86). A possible explanation of this difference is that at gynaecological operations appendicectomy is performed more often as an incidental procedure than in any other type of operation. Also females more commonly have vague abdominal pain due to tubal or ovarian disease, and the appendix is removed because of a mistaken diagnosis. However, even if allowance is made for these there is still a significant sex difference which is inexplicable.

TABLE III

SEX DISTRIBUTION OF PATIENTS WITH TUMOURS

	Female	*Male*
Whole series	365	371
Appendix only	168	86

Incidence of tumours

Carcinoid tumours are not common. Ross (1952) found that they represented 0·18 per cent of all tumours found at necropsy.

Carcinoid tumours of the appendix are not common, but it is the organ that is most often affected. Porter and Whelan (1939) found it to be present in 0·28 per cent (72 in 26,384 appendices). It is, however, the commonest appendicular tumour. Uhlein and MacDonald (1943) reported that of 144 appendicular tumours examined, carcinoids were present in 127 (88·2 per cent).

Gross appearance

Typically, the carcinoid tumour is a submucous plaque situated in the wall of the bowel, varying in size from that of a pin's head to several inches in diameter. Polypoid and annular lesions are seen less commonly. On section the tumour tends to be hard and of bright yellow colour. There is a considerable variation in this colour from pale yellow to orange-brown. This coloration is due to pterins contained within the cell and it is because of this appearance that the diagnosis may be first suspected. Some tumours, or their secondary deposits, may not be pigmented, but this does not seem to alter their degree of malignancy or their biochemical activity.

The growth appears to be well circumscribed, in some cases virtually encapsulated, but this is a false appearance and infiltration can usually be demonstrated microscopically. The tumour may be multiple and in some reports more than sixty plaques of growth were found through the jejunum and ileum (Pennington and Priestley, 1943). The adjacent wall is often thickened with an apparent muscular hypertrophy. This may be compensatory or work hypertrophy produced by subacute intestinal obstruction. It has, however, been demonstrated in gut remnants containing a carcinoid tumour in an ovarian teratoma (Stewart, Willis and de Sarum, 1939). This hypertrophy could be due to the repeated stimulating

The characteristic silver reduction is given by the ammonia-silver impregnation method. This technique does not give constant results, for some areas may be strongly argentaffin whereas adjacent areas show no silver reduction. This finding is probably explained by the fact that all the tumour may not be equally fixed by the formalin. If the tissue is not fixed rapidly after removal from the body it loses its argentaffin reaction. Conversely the longer the formalin-fixed tumour is left before staining the more pronounced is the silver reduction. As mentioned earlier Pearse (1953) believed that the various diazo reactions give more certain results.

Rectal carcinoid tumours are also commonly non-argentaffin staining. Stout (1942) suggested that they develop from a more primitive type of cell, the pre-enterochrome cell. He described them as having a typical appearance—"ribbon-like festoons of columnar and prismatic cells". Morson (1958) has shown that there are three histological types of rectal carcinoid: (1) The "true carcinoids" with granules staining with silver impregnation, and histochemical technique; (2) atypical carcinoids with non-argentaffin granules, but the typical appearance described by Stout (commonest type); and (3) a mixture of the two types, with a minority of granular cells.

Although carcinoids have been regarded as benign or at the most low-grade malignancy they do metastasize widely (Table IV). There is, of course, a great deal of difference in the degree of malignancy. It is most unusual for appendicular tumours to metastasize, whereas those arising in the ileum are more "cancerous" in their behaviour. Most workers agree that these tumours are potentially malignant and would metastasize in time. A possible explanation of the low incidence of malignant appendicular lesions is that this organ is, for some reason, removed before the tumour has had time to spread. It must be pointed out that the average age for the twenty-two malignant appendicular carcinoids selected from the literature was only 26·2 years.

TABLE IV

DISTRIBUTION OF METASTASES IN 286 PATIENTS

Organ	*No. of cases*	*Organ*	*No. of cases*
Lymphatics	180	Omentum	6
Liver	137	Spleen	6
Mesentery	99	Adrenal	5
Peritoneum	52	Mediastinum	4
Bone	11	Kidney	3
Lungs	10	Thyroid	2
Pancreas	10	Testicle	2
Ovary	9	Gall bladder	1
Skin	7	Brain	1

If the figures for the malignant rectal carcinoids are studied it will be seen that there were 18 cases recorded. Ten of these were dead from recurrence within four years. Davies (1959) has suggested that this increased malignancy may be explained by the primitive-cell origin of the tumour.

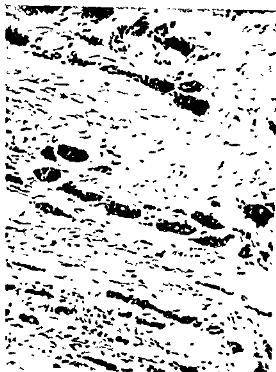


FIG. 16.—Typical appearance of a carcinoid tumour with the well-marked stroma. Tumour of the ileum. (Haematoxylin and eosin. × 100.)

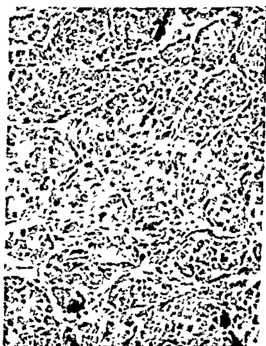


FIG. 17.—Unusual appearance of a carcinoid tumour with virtually no stroma. Tumour of the ileo-caecal valve. (Haematoxylin and eosin. × 100.)



Fig. 18.—Carcinoid tumour of the base of the appendix with a cuff of caecum. This lesion had obstructed the appendicular lumen causing an obstructive appendicitis.

THE FLUSHING SYNDROME

Clinical picture

By the time the patients have developed overt flushing attacks they have permanent telangiectasis over the cheeks and bridge of the nose.

The most dramatic physical sign is the widespread patchy cutaneous flush. It starts in the face, spreading rapidly into the neck, trunk and to the extremities. There is a considerable variation in colour from brick red to cyanotic, with intervening areas of pallor. The patches vary in size, some are several inches in diameter, whereas others are á mere pin-point size. The duration of the flush is usually only 2–3 minutes, but in some patients it will last longer and in others a bluish mottled appearance lasts for most of the day.

The flushing attacks may occur at any time but are frequently related to bodily functions. Eating, drinking and defaecation commonly provoke the flush. Alcohol, both orally and parenterally, causes attacks as does emotion, particularly embarrassment or anger. Manipulation of the tumour will often produce a flush, and at operation or barium enema may result in sudden collapse of the patient.

Coincidentally with its onset, patients experience many unpleasant subjective sensations. They feel hot, complain of palpitations, and of a feeling of fullness in the head, which may amount to giddiness and blurring of vision. They have

SYMPTOMATOLOGY

Forbus (1925), after reviewing the literature, wrote in his summary "attention is called to the general harmless character of the argentaffin tumors". He expressed the opinion of the majority of workers at that time. As the years passed, however, it became increasingly obvious that these tumours were not as benign as originally thought and were certainly not asymptomatic.

Reviewing the world literature Davies (1959) collected 705 cases of benign and malignant carcinoid tumours. He found that 431 (62 per cent) had symptoms directly referable to the tumour.

Grimes and Bell (1949) considered that there was a tetrad of symptoms: (1) partial gut obstruction; (2) pain; (3) diarrhoea; and (4) weight loss. To this list we must now add the flushing attacks.

Malignant small gut growths present most commonly with obstruction. Cooke (1931) found that although only 7 per cent of the benign lesions obstructed, 50 per cent of the malignant ones presented in this way. The common type of tumour, the intramural plaque, is usually too small to occlude the lumen. Obstruction is more likely to occur with the less common annular or polypoid lesions. As the tumour infiltrates it promotes the fibroblastic reaction that has been described above. Such a reaction leads to shortening of the mesentery which may produce an acute angle or "kink" of the gut leading to obstruction. Cases have been described where the cause of the obstruction has been an intussusception with a carcinoid tumour, usually a polyp, as the apex. Some of these lesions have been resected with ultimate recovery of the patient (Diffenbaugh and Anderson, 1956).

Tumours located in the stomach and duodenum have given rise to epigastric discomfort suggestive of peptic ulceration.

Appendicular pain can be caused by locally occurring carcinoid tumours. A lesion situated at the base of the appendix, or in some position where it can occlude the lumen, may give rise to an obstructive appendicitis (Fig. 18). Usually the tumour is at the tip where it could not cause very much trouble, and is found incidentally. Masson (1928) believed that chronic abdominal pain could be caused by the presence of the carcinoid tumour. He considered that it was due to neuromas formed when argentaffin cells penetrated the nerve sheaths.

Colicky abdominal pain may also occur without any apparent obstruction that could be demonstrated subsequently at operation. Frequently it is accompanied by severe diarrhoea. It has been suggested that intestinal colic and hyperperistalsis are due to muscle stimulation by the large concentrations of 5-HT being liberated either locally by the tumour or present in the circulating blood. Diarrhoea is a very common symptom and can reach such proportions that it is completely crippling. It is not accompanied by melaena for it is most unusual for gross surface ulceration to occur.

Weight loss may occasionally be extreme but usually it is not as severe as the cachexia seen with other types of cancer of comparable dissemination.

Uncommonly patients have presented with haematemesis and melaena (Adamson and Postlethwaite, 1958), palpable tumours (O'Brien, 1951), and spontaneous fracture of the hip (Barnes, 1952).



Fig. 19.—The pulmonary valve with a moderate degree of stenosis.

Fig. 20.—The right side of the heart showing the changes in the tricuspid valve and the areas of endocarditis in the right atrium.



borborygmi, gut colic and often a bowel movement. The bladder is similarly affected and there is an urgent desire to micturate. These patients frequently have asthmatic-like attacks of varying severity at the time of the flushes.

There are marked temperature gradients between the bright red flushed areas and the adjacent pallid areas. Thorson and his colleagues (1954) recorded differences of 9°C. between the adjacent skin areas.

Thorson (1956) described the haemodynamic changes occurring during these attacks. He considered that the flush could be divided into three stages.

Stage 1—lasting 20 seconds. Reddening and burning of the face, spreading rapidly down to the trunk and into the limbs. The pulse becomes weak and irregular with decreased heart sounds.

Stage 2—lasting several minutes. The flush is fully developed and there is a rapid pulse and high systolic and pulse pressures.

Stage 3—there is usually a transition stage where the flush becomes patchy, and eventually cyanotic. The pulse becomes weak, with a high systolic pressure and low pulse pressure.

Not all the flushes fall into this pattern, particularly in regard to Stage 3—the cyanotic phase. It has been seen that the degree of cyanosis varies considerably and bears some relationship to the environmental temperature. On cold days the cyanotic stage predominates whereas on hot days it may be completely absent (Davies, 1959).

In all attacks of flushing there is an increased respiratory rate. In some cases there is expiratory difficulty which can be of sufficient severity to amount to a classical asthmatic attack.

In cases where the heart lesions are advanced there is frequently congestive heart failure with oedema complicating the clinical picture.

Pathological changes

The vessels in the skin show marked changes. The capillaries are dilated with thickening of the walls. A similar appearance is seen in the venules and to a lesser degree in the arterioles.

Sometimes the patient will exhibit brown scaly areas of desquamation particularly on the back. These are very much like pellagrinous skin lesions, and are almost certainly due to disturbance of nicotinic acid formation.

The length of survival depends on the presence and severity of the lesions of the heart valves. Patients with the most extensive liver involvement survive for many years. The author knows of one patient with a carcinoid tumour involving his bile duct and pancreas who has survived for 20 years. Patients suffering from the flushing syndrome eventually die as a result of their heart lesions rather than as a direct result of their tumour (Table V).

TABLE V

DISTRIBUTION OF VALVE LESIONS

No. of cases with flushing	42
No of cases with valve lesions	29
Pulmonary valve	29
Tricuspid valve	18
Aortic and mitral valves	4

Possible causes of the flushing syndrome

Many theories have been advanced to explain both the cutaneous vasomotor phenomenon and the valvular changes. The evidence available suggests that the changes are promoted by some humoral mechanism affecting the whole vascular system, although only the skin changes are obvious. Since Lembeck (1953) extracted 5-HT in large quantities from carcinoid tumours it could be that this substance is responsible for the cardiovascular changes.

Roddie, Shepherd and Whelan (1955) gave intra-arterial injections of 5-HT and reproduced the flush which was followed by cyanosis in the peripheral part of the limb. Other workers have been able to reproduce all the other symptoms experienced during the flush by administering large quantities of 5-HT intravenously. 5-HT is destroyed in the lungs and perhaps this explains the occurrence of right-sided valve lesions. Goble, Hay and Sandler (1955) compared 5-HT levels sampled from the pulmonary artery and brachial artery. They found levels of 5·6 micrograms per millilitre in the pulmonary vessel but only 1·9 micrograms per millilitre in the peripheral artery. Two possible findings may explain the occasional occurrence of left-sided valve lesions. In two patients a patent foramen ovale was demonstrated at necropsy. Both had pulmonary stenosis which, by increasing the right heart pressure caused a right-to-left shunt through the patent foramen (McKusick, 1956; Wolfe, and his colleagues, 1960). Another patient had well-developed pulmonary metastases (Goble, Hay and Sandler, 1955). Both these mechanisms could have delivered sufficient 5-HT into the left heart blood to produce the lesions.

The cause of the valve lesions is not known. It has been demonstrated that 5-HT leads to pulmonary vasoconstriction and there is a corresponding rise in pressure in the right side of the heart. Thorson (1956) suggested that this repeated stretching of the heart structures eventually brings about the endocardial changes. An alternative theory is that it is due to a direct chemical effect on the endocardium. The higher incidence of right-sided lesions is explained by the fact that the valves are bathed in blood containing abnormal concentrations of 5-HT. The occurrence of the occasional left-sided lesions are additional evidence in favour of this theory. 5-Hydroxytryptamine does cause an alteration in cell permeability and thus the formation of oedema which could then fibrose and organize.

The valve lesions are progressive. Many examples of the slow development of the pulmonary stenosis whilst the patient has been under observation have been recorded.

5-Hydroxytryptamine is a histamine liberator. Pernow and Waldenstrom (1957) found that some of their patients had abnormal levels of histamine in the blood and urine. Other workers, however, have found normal histamine levels in all their patients (Snow and his colleagues, 1955).

Patients excreting large quantities of 5-HIAA will sometimes pass urine that on standing for a few minutes in the light becomes burgundy coloured. This is due to pigment formation occurring at the 5-HT–5-HIAA stage of metabolism. On the days that the urine contains these large quantities of pigment the levels of 5-HIAA excretion in the urine are depressed, sometimes to normal levels.

The pulmonary valve is most commonly involved. The cusps are thickened, with rolling of the edge, and are fused forming a stenosis (Fig. 19). It is an appearance which is unlike the congenital defect. There is sometimes endocardial thickening in the infundibulum and also in the walls of the small pulmonary arteries. The tricuspid valve is also frequently involved. It is rendered incompetent by contraction of the papillary muscle and chordae tendineae. There is also beading and thickening of the valve margin and if this change predominates stenosis will result (Fig. 20). The endocardium in the right atrium and ventricle often have plaques of endocarditis.

Valvular lesions in the left side of the heart are most unusual. Aortic and mitral lesions have been reported only on a few occasions. In none of these cases was there a history of rheumatic fever or syphilis (Goble, Hay and Sandler, 1955; McKusick, 1956).

Microscopically the valve lesions consist of a poorly standing deposit of fibrous tissue "plastered" over the surface of the valve. There is no inflammatory reaction and the underlying valve endocardium is completely normal, except that there may be large numbers of mast cells (Fig. 21). The microscopic appearance is completely unlike that of chronic rheumatic or syphilitic endocarditis.



FIG. 21. — Tricuspid valve. (Haematoxylin and eosin. ×10.)

anaesthesia combined with chlorpromazine as a pre-medication might be safer. The latter substance is a 5-HT antimetabolite, and so on empirical grounds might be of value. The epidural anaesthetic is believed to act in two ways; first, on absorption of the local anaesthetic there is bronchodilatation and, secondly, it reduces venous return and so prevents the development of pulmonary hypertension.

Irradiation

It is generally accepted that external irradiation has no place in the treatment of these tumours. Only a few successful cases have been reported (Ariel, 1939).

Goble, Hay and Sandler (1955) reported symptomatic improvement and a transient decrease in the excretion of 5-HIAA following the administration of radioactive gold to a patient with the syndrome. This patient had hepatic metastases and the radioactive gold, absorbed into the reticulo-endothelial system, was able to irradiate in close proximity to the tumour. It is not likely, however, that this method could be applied therapeutically.

Drug therapy

Nitrogen mustard

Only one report has been made concerning regression of tumours following the administration of nitrogen mustard (Eldred, 1956). Nitrogen mustard is more active against the proliferative type of lesion but whether it could have a significant cytotoxic effect on the slowly growing carcinoid tumour is doubtful.

Antimetabolites

5-Hydroxytryptamine has many antimetabolites that are powerful antagonists in experimental conditions. However some of these, for example, yohimbine and adrenochrome, have pronounced psychic side-effects and could not be used therapeutically.

Lysergic acid diethylamide.—This has been used on many occasions. No improvement that could be attributed solely to the drug has been recorded. Patients under treatment experienced unpleasant side-effects. A brominated derivative (BOL 148) has been prepared and was found to be free from these complications (Cerletti and Rothlin, 1955). This, too, is active *in vitro*, but again inactive in patients.

Ergotamine

Members of the ergonovine group have been tried without success.

Methyl serotonins

The methyl serotonin group of compounds were first investigated by Woolley and Shaw (1952) in an attempt to control essential hypertension. It was found, however, that there was no improvement in the blood pressure level (Spies and Stone, 1952). In 1956 Woolley and Shaw synthesized 1 benzyl 2·5 dimethyl serotonin which was found to have a protective action against the pressor effects of 5-HT. This substance has also been used in an attempt to control the systemic effects of 5-HT in the flushing syndrome. Doses of 150–400 milligrams per day produced no alteration of the symptoms, but it was noted that it had a tranquillizing effect.

DIAGNOSIS

Before the significance of the flushing syndrome had been recognized the pre-operative diagnosis of carcinoid tumours was rarely made. Miller and Herrmann (1942) demonstrated the "kinking" of the bowel at the site of the tumour, during barium studies. Their diagnosis was confirmed at subsequent operation.

Since the flushing syndrome has been recognized the correct diagnosis is often made. Many methods for the estimation of 5-HT in the blood and of 5-HIAA excreted in the urine have been devised. It is technically easier to estimate 5-HIAA in the urine, hence this method is used in most clinical laboratories. Chromatographic methods are also widely used (Jepson, 1955).

TREATMENT

Surgical

The operative treatment of a carcinoid tumour presents many problems. Obviously it should be treated as any malignant growth, by wide excision of the primary and the local lymphatic field if technically possible. However, its true nature may not be apparent at operation and if deemed inoperable some minor procedure may have been performed to relieve or prevent obstruction. Often the tumour occurring in the appendix is not seen when removed, and only subsequently demonstrated by histological examination. Davies (1959) suggested that future management of the patient should be guided by the pathological findings. If the tumour is found to reach the limit of section of the mesentery or mesoappendix, or if lymphatics or blood vessels are involved then further operative treatment is indicated. At this procedure further resection can be carried out. LeConte (1908) reported a patient with a "carcinoma" of the appendix who was re-explored and a right hemicolectomy performed. The ileo-caecal glands were found to contain metastatic growth.

Grimes and Bell (1949) compared the survival times of eight patients with malignant small gut lesions. They found that if a wide resection had been performed the patients survived for eight years; if the lesion was "by-passed" they survived four years. If the lesion was biopsied only, there was a 12 month survival. Although, admittedly, their series is too small to be of great value it does give an indication of the survival times. Other workers have reported long survival even in the presence of widespread metastases (Stewart and Taylor, 1926).

It would not be unreasonable to presume that the onset and severity of the flushing syndrome is related to the amount of tumour tissue present in the body. The removal of metastases should stop or postpone the development of the cardiovascular changes. Widespread resection of metastases, even hepatic lobectomy has been advocated (Wilson and Butterick, 1959). Thorson and his colleagues (1958) reported the disappearance of the flushing and diarrhoea following removal of a carcinoid tumour contained in an ovarian teratoma; however, the valve lesions did not regress.

A further difficulty may arise during the administration of the anaesthetic. It has been found that patients suffering from the flushing syndrome develop a bronchoconstriction that resists both ether and pethidine. Massaging or handling the tumour has caused collapse of the patient. It would appear that epidural

Antihistamines

Feldberg and Smith (1953) demonstrated that 5-HT was a histamine liberator. It has been shown quite conclusively that some patients with the flushing syndrome do excrete abnormal quantities of histamine (Pernow and Waldenstrom, 1957). In view of this finding antihistaminic drugs were administered. There was again no clinical improvement that could be attributed to the drug.

Symptomatic treatment

Normally 1 per cent of the tryptophan intake is utilized for 5-HT production, but in carcinoidosis 60 per cent is deviated (Udenfriend, Weissbach and Sjoerdsma, 1956). Tryptophan is concerned with nicotinic acid formation, and deviation of this amino acid has lead to vitamin deficiency. Cases have been reported where patients have developed pellagra which has been cured by the administration of niacin (Thorsen and his colleagues, 1958).

Mental changes also occur especially in the terminal stages of the disease. This could be related to the pellagrinous state or to the very high levels of 5-HT in the cerebral circulation. It has not been possible to improve the mental state by administering niacin.

As the flushing syndrome progresses the valvular lesions lead to heart failure with resultant oedema and ascites. Treatment with diuretics will usually control this condition.

Diarrhoea is the most distressing symptom. It is, moreover, extremely difficult to control using the usual medical remedies, and none of the antimetabolites of 5-HT has the slightest effect.

CONCLUSION

Not all patients suffering from carcinoidosis develop the flushing syndrome. The reason for the different behaviour is not understood, for histologically the tumours appear to be identical. The valvular lesions are commonly responsible for the death of the patient from heart failure, for even with extensive hepatic involvement patients can survive many years.

At operation it may be possible to resect much of the tumour masses. This procedure should postpone the development of the flushing syndrome or bring about some amelioration of the symptoms.

Antimetabolite therapy has been given an adequate clinical trial and has failed to influence the course of the lesions. An alternative therapy, using anti-enzymic substances, for example phenylacetic acid, has given disappointing results. There is, however, the possibility that substances of similar chemical nature may be more readily absorbed and thus able to reach the tumour and give better results.

REFERENCES

Adamson, J. E., and Postlethwaite, R. W. (1958). *Ann. Surg.* **148**, 239.
Ariel, I. M. (1939). *Arch. Path.*, **27**, 25.
Barnes, T. G. (1952). *Surgery*, **32**, 723.
Barter, R., and Pearse, A. G. E. (1955). *J. Path. Bact.*, **69**, 25.

Chlorpromazine

Benditt and Rowley (1956) reported that chlorpromazine antagonized the action of 5-HT in animal experiments. Cole and Bertino (1956) administered 25 milligrams 6 hourly for 4 days to a patient with the flushing syndrome. They recorded that there was an immediate depression in urinary excretion of 5-HIAA and a decrease in the number of stools per day. This work has been repeated, but their results have not been confirmed. It has been demonstrated that the decrease in urinary 5-HIAA was only apparent and was due to a direct quenching of the colour reaction by the chlorpromazine.

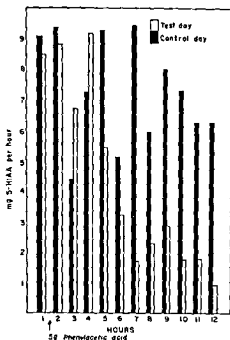


Fig. 22.—The hourly excretion of 5-hydroxyindole acetic acid after administration of phenylacetic acid.

Anti-enzymes

Pare, Sandler and Stacey (1958) recorded that in phenylketonuria the level of 5-HT in the serum was depressed. It was suggested that this was due to circulating aromatic acids depressing some part of the enzyme system, possibly 5-hydroxytryptophan decarboxylase. One of the acids, phenylacetic acid, is known to be safe for oral administration up to 15 grammes per day (Sherwin and Kennard, 1919). Sandler, Davies and Rimington (1959) administered 5 grammes per day of phenylacetic acid to several patients with the flushing syndrome. They found that there was no constant clinical improvement but there did appear to be a depression of 5-HIAA excretion. This decline started in the second or third hour after administration of the drug, and continued for many hours (Fig. 22). They suggested that the lack of symptomatic improvement may be due to the relative inaccessibility of much of the tumour tissue to the circulating drug.

Ross, C. F. (1952). *Brit. J. Surg.*, 40, 248.
Sandler, M., Davies, A. J., and Rimington, C. (1959). *Lancet*, **2**, 318.
Semsroth, K. (1928). *Arch. Path.*, 6, 575.
Sherwin, C. P. and Kennard, K. S. (1919). *J. biol. Chem.*, 40, 259.
Smith, A. N., Nyhus, L. M., Dalgleish, C. E., Dutton, R. W., Lennox, B. and Macfarlane, P. S. (1957). *Scot. med. J.*, **2**, 24.
Snow, P. J. D., Lennard-Jones, J. E., Curzon, G. and Stacey, R. S. (1955). *Lancet*, **2**, 1004.
Spies, T. D., and Stone, R. E. (1952). *J. Amer. med. Ass.*, **150**, 1599.
Stewart, M. J., and Taylor, A. L. (1926). *J. Path. Bact.*, **29**, 136.
— Willis, R. A., and de Saram, G. S. W. (1939). *Ibid.*, 49, 207.
Stout, A. P. (1942). *Amer. J. Path.*, **18**, 993.
Thorson, Å. H. (1956). *Amer. Heart J.*, **52**, 444.
— Biorck, G., Bjorkman, G., and Waldenstrom, J. (1954). *Ibid.*, **47**, 795.
— Hansen, A., Pernow, B., Soderstrom, N., Waldenstrom, J., Winblad, S., and Wulff, H. B. (1958). *Acta med. scand.*, **161**, 495.
Toennissen, E. (1909). *Z. Krebsforsch.*, **8**, 355.
Trappe, M. (1907). *Frankfurt Z. Path.*, **1**, 109.
Udenfriend, S., Weissbach, H., and Sjoerdsma, A. (1956). *Science*, **123**, 669.
Uhlein, A. and MacDonald, J. R. (1943). *Surg. Gynec. Obstet.*, **76**, 711.
Vialli, M., and Erspamer, V. (1937). *Bull. Soc. méd-chir. Pavia*, **51**, 1111.
Wilson, H. and Butterick, O. D., Jnr. (1959). *Ann. Surg.*, **149**, 641.
Wolfe, H. R. I., Davies, A. J., and Schacter, M. (1960). *Brit. med J.*, **1**, 295.
Woolley, D. W., and Shaw, E. N. (1952). *J. Amer. chem. Soc.*, 74, 2948.
— — (1954). *Brit. med. J.*, **2**, 122.
— — (1956). *Science*, **124**, 34.
Wyatt, T. E. (1938). *Ann. Surg.*, **107**, 260.

SELECTED ABSTRACTS

Carcinoid syndrome

Effect of phenylacetic acid

Sandler, Davies and Rimington (1959) refer to the production of serotonin by carcinoid tumours. With the object of limiting the local formation of the amine the authors employed the relatively non-toxic phenylacetic acid in the management of five patients suffering from the carcinoid syndrome. The dose of the drug ranged from 2·5 to 6 grammes daily. In two cases phenylacetic acid or a placebo, in doses of 6 grammes daily, were allocated on 14 successive days to make a total of 7 days of each treatment. No patient complained of the unpleasant odour of the drug. The first patient, a man aged 63 years, had a history of diarrhoea for five years, pain in the lower part of the abdomen for two years, and attacks of flushing for six months. The urine contained large quantities of 5-hydroxyindole acetic acid. According to the patient, diarrhoea was less pronounced when phenylacetic acid was administered, but this observation was not confirmed by the double-blind studies. The second patient was a woman aged 58 years. Diarrhoea was relieved by the treatment, but the attacks of flushing persisted. In the third case phenylacetic acid therapy failed to produce any improvement. In fact, the treatment seemed to lead to a mental disability which resembled that of alcoholic intoxication. As nausea and vomiting developed in the fourth case, treatment with the drug was discontinued. The last patient believed that use of the drug had relieved the flushes. As in the first case, this observation was not confirmed by the investigators. With reference to laboratory tests, specimens of urine were obtained for periods of 12 hours by means of an indwelling catheter. Decrease in the excretion of 5-hydroxyindole acetic acid was detected in 3 cases, a finding which was compatible with the inhibitory effect of phenylacetic acid upon 5-hydroxytryptophan decarboxylase.

Benditt, E. P., and Rowley, D. A. (1956). *Science*, **123**, 24.
Bigelow, F. S. (1953). *J. clin. Invest.*, **32**, 555.
Biorck, G., Aken, O., and Thorson, A. H. (1952). *Amer. Heart J.*, **44**, 143.
Boyland, E., Gasson, J. E. and Williams, D. C. (1956). *Lancet*, **2**, 975.
Bulbring, E., and Lin, R. C. Y. (1958). *J. Physiol.*, **140**, 381.
Bunting, C. H. (1904). *Johns Hopk. Hosp. Bull.*, **15**, 89.
Cassidy, M. (1930–31). *Proc. R. Soc. Med.*, **24**, 139 and 920.
— (1933–34). *Ibid.*, **27**, 220.
Cerletti, A., and Rothlin, E. (1955). *Nature, Lond.*, **176**, 785.
Cole, J. W. and Bertino, G. G. (1956). *Proc. Soc. exp. Biol., N.Y.*, **93**, 100.
Cooke, H. H. (1931). *Arch. Surg.*, **22**, 568.
Davies, A. J. (1959). *Ann. R. Coll. Surg., Engl.* **25**, 277.
Diffenbaugh, W. G., and Anderson, R. E. (1956). *Arch. Surg.*, **73**, 21.
Dockerty, M. B., and Ashburn, F. S. (1943). *Arch. Surg.*, **47**, 221.
Ehrlich, S. L. (1912). (Quoted by P. Masson, 1928.) *Amer. J. Path.*, **4**, 181.
Eldred, W. J. (1956). *Arch. Surg.*, **73**, 517.
Engle. (1923). (Quoted by W. D. Forbus, 1925). *Johns Hopk. Hosp. Bull.*, **37**, 130.
Erspamer, V. (1954). *Pharmacol. Rev.*, **6**, 425.
— Asero, B. (1952). *Nature, Lond.*, **169**, 800.
Feldberg, W., and Smith, A. N. (1953). *Brit. J. Pharmacol.*, **8**, 406.
Forbus, W. D. (1925). *Johns Hopk. Hosp. Bull.*, **37**, 130.
Goble, A. J., Hay, D. R. and Sandler, M. (1955). *Lancet*, **2**, 1016.
Grimes, O. F., and Bell, H. G. (1949). *Surg. Gynec. Obstet.*, **88**, 317.
Hamlin, K. E., and Fischer, F. E. (1951). *J. Amer. chem. Soc.*, **73**, 5007.
Haverback, B. J., Dutcher, T. F., Shore, P. A., Tomich, E. G., Terry, L. L., and Brodie, B. B. (1957). *New Engl. J. Med.*, **256**, 343.
Isler, P., and Hedinger, C. (1953). *Schweiz. med. Wschr.*, **83**, 8.
Jepson, J. B. (1955). *Lancet*, **2**, 1009.
Kultschitzky, N. (1897). *Arch. mikr. Anat.*, **49**, 7.
LeConte, R. G. (1908). *Trans. Amer. surg. Ass.*, **26**, 445.
Lembeck, F. (1953). *Nature, Lond.*, **172**, 910.
Lewis, D., and Geschickter, C. F. (1934). *Arch. Surg.*, **28**, 16.
Lubarsch, O. (1888). *Virchows Arch.*, **3**, 280.
Masson, P. (1928). *Amer. J. Path.*, **4**, 181.
McKusick, V. A. (1956). *Johns Hopk. Hosp. Bull.*, **98**, 13.
Miller, E. R., and Herrmann, W. W. (1942). *Radiology*, **39**, 214.
Millman, S. (1943). *Amer. Heart J.*, **25**, 391.
Milne, W. L., and Cohn, S. H. (1957). *Amer. J. Physiol.*, **189**, 470.
Morson, B. C. (1958). *In Modern Trends in Gastro-enterology* (2nd series). Ed. by F. Avery Jones p. 107. London; Butterworth.
Obendorfer, S. (1907). *Frankfurt, Z. Path.*, **1**, 426.
O'Brien, J. R. (1951). *Brit. med. J.*, **2**, 1315.
Page, I. H. (1958). *Physiol. Rev.*, **38**, 277.
— McCubbin, J. W. (1953). *Circulat. Res.*, **1**, 354.
Pare, C. M. B., Sandler, M. and Stacey, R. S. (1958). *Lancet*, **2**, 1099.
Pearse, A. G. E. (1953). *Histochemistry, Theoretical and Applied.* London; Churchill.
Pennington, R. E., and Priestley, J. T. (1943). *Proc. Mayo Clin.*, **18**, 49.
Pernow, B. (1958). *In Modern Trends in Gastro-enterology*, (2nd series). Ed. by F. Avery Jones. p. 101. London; Butterworth.
— Waldenstrom, J. (1957). *Amer. J. Med.*, **23**, 16.
Porter, J. E. and Whelan, C. S. (1939). *Amer. J. Cancer*, **36**, 343.
Raiford, T. S. (1933). *Amer. J. Cancer*, **18**, 803.
Ransom, W. B. (1890). *Lancet*, **2**, 1021.
Rapport, M. M., Green, A. A. and Page, I. H. (1948). *Science*, **108**, 329.
Roddie, J. C., Shepherd, J. T. and Whelan, R. F. (1955). *Brit. J. Pharmacol.*, **10**, 445.

pulmonary regurgitation, and right ventricular failure during a spontaneous flush. The findings in this patient, and in three others patients with the carcinoid syndrome and darkish red flushes, showed that periodic dilatation of the right ventricle occurs in at least some cases. The findings at necropsy included fibrotic epicardium and pericardium which were adherent to each other, dilatation of both atria and the right ventricle, and a tricuspid ostium, which permitted the passage of two fingers. The endocardial lesions may be due to several mechanisms, including sudden distension of the endocardial structures in the right side of the heart repeated during several years, a local action of 5-hydroxytryptamine which might alter the endothelial permeability, and deposition of fibrin and platelets on the endothelium. Other possible factors are the lowered tissue resistance against trauma due to the altered tryptophan metabolism with hypoproteinaemia and hypovitaminosis in carcinoid disease. The authors emphasize that these patients are not suitable for valvotomy, and that opiates to alleviate the diarrhoea should be used only with caution when there is a small diuresis.

Vasculocardiac syndrome

BEAN and FUNK (1959) presented a case of the vascular syndrome caused by hyperserotoninaemia produced by a metastatic carcinoid tumour in the liver. A male patient, aged 57 years, gave a history of having suffered nine years previously from haemorrhoids and intermittent diarrhoea; two years later, following an automobile accident, he became agitated and nervous, and experienced cramps and abdominal pains. Radiography revealed, 3½ years prior to admission to hospital, spastic colitis and diverticulitis for which treatment, including special diet, antispasmodics and antibiotics, was given without effect. He had no symptoms of heart disease prior to admission. The skin revealed tiny telangiectases; superimposed on a persistently florid complexion was a transient waxing and waning of erythema which gradually became more spectacular. While in hospital the patient had increasing oedema, vomiting and psychosis, and symptomatic therapy had little effect. He became gradually worse and died approximately 16 months after being first examined. The main necropsy findings were a small nodule in the ileum, with gross metastases to the regional lymph nodes and the liver, which was almost entirely replaced by nodules and by tumour tissue, hypertrophy of the right ventricle and thickening of the tricuspid and pulmonary valves; the mitral and aortic valves were also involved; the coronary arteries were atherosclerotic but there was no myocardial infarct. The tumour nodules had the microscopic structure of an argentaffinoma. The authors have not seen pellagra in the three cases of the syndrome which they have observed; if it occurs, they would ascribe it to the losses of vitamins from hypermotile diarrhoea. Antagonists to serotonin have been suggested as a possible treatment for the syndrome, but were given ineffectively in the present case. A feature of the case was very dense and hard fibrosis from adhesions following an abdominal operation which the patient had undergone. The authors consider that this reaction, and the general increase in collagen, fibrinoid, and hyaline material suggest speculations regarding the pathogenesis of such various diseases as cirrhosis of the liver and systemic lupus erythematosus.

Carcinoid of the ampulla of Vater

As yet only five cases of carcinoid of the ampulla of Vater have been recorded in the literature. The series include two cases described by MCCRAE and CONN (1959). One patient was a man, aged 57 years, with a history of generalized pruritus and intermittent jaundice. Operation revealed an enlarged gall-bladder and a dilated common bile duct. Choledochostomy was performed and the duodenum was opened anteriorly. A mass 1·5 centimetres in diameter was resected at the ampulla of Vater. Both the common duct and the duct of Wirsung were transected and re-approximated to the duodenum. Histological examination showed the presence of carcinoid in the mass and in a lymphatic gland which had been removed from the vicinity of the second part of the duodenum. Another patient, a man aged 69 years, had suffered from intermittent attacks of abdominal pain, jaundice and fever. Wide excision of the tumour was performed and the common duct was re-

Resection of secreting carcinoid

Relief of flushing

It is only recently that the syndrome caused by the endocrine activity of metastatic argentaffinomas or carcinoids has been recognized, and in most reported cases the metastases were hepatic, with few opportunities for observing cessation of endocrine activity after removal of a tumour mass. POLLOCK (1959) recorded a case in which the symptoms disappeared after the removal of a large mass of mesenteric lymph nodes which were the seat of an argentaffinoma from a primary tumour in the mid-ileum. The diagnosis of secreting argentaffinoma was confirmed by the finding of grossly elevated 5-hydroxyindole acetic acid (5-HIAA) levels in 24-hour specimens of urine; these ranged from 35 to 110 milligrams in 24 hours, the upper limit of normal by the method used being 10 milligrams in 24 hours. The increased urinary excretion of 5-HIAA indicated an increased production of 5-hydroxytryptamine. The fact that this substance was being produced by the mesenteric node metastases and not by liver metastases was demonstrated by the rapid return of 5-HIAA levels to normal, and the disappearance of the hot flushes which the patient had experienced, following excision of the primary tumour and the mesenteric nodes. An interesting feature in the present case is the duration of symptoms, 19 years, although one patient in a reported series had flushes for 20 years.

Vasomotor reactions secondary to malignant carcinoid

Control by massive liver resection

WILSON and BUTTERICK (1959) discussed massive liver resection for the control of severe vasomotor reactions secondary to malignant carcinoid. The serotonin produced by the malignant carcinoid which causes the vasomotor and vascular changes is generally thought to be counteracted or "detoxified" by the liver. The vasomotor symptoms, therefore, are not seen in patients with malignant carcinoid as long as the tumour is confined to the intestinal tract. The authors present a case in which a striking alleviation of the vasomotor symptoms was achieved by removing a large amount of the malignant carcinoid tissue from the liver. Examination of the removed liver tissue showed a serotonin content of 0·57 milligram per gramme; although the patient still experiences occasional flushing of the face, he has not had the extreme weakness or dyspnoea which he had before the operation, and he has returned to strenuous full-time work. A second case is presented which, although it failed in the above objective, provided further pathological proof of the changes which occur in the right heart in patients suffering from this disease. The patient died approximately six days post-operatively, and necropsy revealed considerable stenosis and insufficiency of the tricuspid valves and fusion of the pulmonary valves; the chordae of the valves showed small fibrous nodules and there was subendothelial fibrosis involving the valves and other areas of the right heart.

Metastatic carcinoid disease

Development of valvular lesions

The development of valvular lesions in metastatic carcinoid disease are discussed by THORSON and NORDENFELT (1959). A female patient aged 51 years was admitted to hospital with a carcinoid tumour of the jejunum and extensive metastases. Her symptoms, which included abdominal pain, hot flushes, red discoloration of the skin, diarrhoea, cyanosis, loss of weight and palpitation, had begun 10 years prior to the operation. Her medical history included an operation for cholelithiasis 11 years before the present admission to hospital. She died three years after the operation for removal of the primary jejunal tumour and metastases, apparently from congestive heart failure. Examination of the heart prior to the second operation had revealed haemodynamic changes during the flush episodes: the sounds became weak, and the I, J and K waves of the displacement ballistocardiogram became lower than before the flush; when the red colour of the skin was fully developed and stationary, the sounds became loud and an atrial sound was audible. The changes included episodic increases of the venous return and dilatation of the right side of the heart; catheterization demonstrated tricuspid regurgitation, probable

more than ten times that in canine blood and more than thirty times that in human specimens. There is apparently little, if any, serotonin in the lungs of cats, dogs or humans. It was found that the pressure changes due to thromboembolism in the anaesthetized dog could be due to mechanical occlusion and did not resemble the changes due to serotonin injections. The authors say that since the amount of serotonin in human blood is less than that of the dog, the role of serotonin in human pulmonary thromboembolism is probably very slight indeed.

Postgastrectomy patients

Psychiatric observations

A follow-up was made of 105 postgastrectomy patients and 50 of the 105 were interviewed for one hour by ROND (1959) for a psychiatric evaluation. All patients had had Billroth I operation with bilateral vagotomy for duodenal ulcer. None of the 50 patients showed recurrence of ulcer. Their ages were between 30 and 70 years; they were from all social levels, and at least one year had passed since operation when the patients were seen. The cases were divided into: Group 1—25 patients all of whom were very pleased with their operations. Group 2—15 patients: these were pleased but complained of gastro-intestinal disturbances. Group 3—4 patients: these were overtly anxious complainers. Group 4—6 patients: these were not satisfied with the operation and had gastro-intestinal complaints as well as being emotionally upset. Rond says the reaction to the operation is an important factor in the overall results. The ulcer itself as a major source of discomfort is also of importance. The surgeon takes on all cases, emotionally speaking, and his results are reflected in the lives of his patients. This investigation shows that emotional factors such as distressing experiences have an active effect both pre-operatively and post-operatively on the lives of duodenal ulcer patients. It was noted that changes in the patient's life could change a poor result into a satisfactory one. Two illustrative cases were quoted; both the patients were not so well after operation, but recovered completely when the cause of their emotional stress was removed. A poor prognosis was indicated by the early onset of abdominal pain. Many patients with this history had poor results of operation. Rond concludes that in a stable personality the removal of the ulcer leads to excellent results. If the patient is unstable only poor results follow. In the adequate person the postgastrectomy syndrome may appear, with or without complaint; the syndrome may clear up with later marked emotional changes. Further psychiatric study is needed of the dumping syndrome in relation to emotional factors.

Acute small bowel obstruction

Treatment

A review of 493 cases of acute small bowel obstruction, seen during the period 1935–1957, is presented by HOYER and SOLHEIM (1959). The series comprised 265 females and 228 males: 110 of the patients had strangulation, 38 were not operated upon, and in 16 cases the obstruction gave way spontaneously during pre-operative therapy. There were 47 deaths among patients operated upon and 10 among those not operated upon. In the pre-operative treatment correction of the loss of fluids and electrolytes was routine throughout the whole period: on the average, each patient received 2,330 millilitres of fluids; the greatest amount given to any single patient was 9,000 millilitres. The anaesthesia used in the first 17 years was spinal, and in the last 6 years it was general. The obstruction was due to bands without strangulation in 114 cases, bands with strangulation in 81, adhesions in 155, Meckel's diverticulum in 16, incarceration in internal hernias in 14, volvulus in 12, intussusception in 16, gall-stones in 5, alimentary obstruction in 16, and intraperitoneal abscess in 6; 318 of the patients had undergone a previous laparotomy. The cause of death in 21 cases was peritonitis, and the causes in other cases included shock, paralytic ileus, pneumonia, cardiac insufficiency, pulmonary embolism, abdominal wall inflammation, acute pancreatic necrosis, small bowel fistula, and lower nephron nephrosis. The duration of disease on admission was 1–12 hours in 172 patients, of whom 9 died, and over 96 hours in 40 patients, of whom 11 died. The results of the study demonstrate that early

implanted into the duodenum. After discharge from hospital both patients continued to be free from symptoms and the serotonin values remained within normal limits. With reference to tests for serotonin, the tumour cells resemble those of the chromaffin tissue of paraganglia and it is believed that serotonin is produced by the chromaffin cells of the intestinal tract. As for the surgical management of carcinoid of the ampulla of Vater resection should be performed even when metastases are present in the liver, for the tumour is slow growing and the life expectancy is good. At the same time it is to be noted that duodenal obstruction may eventually occur if the tumour is not removed.

Carcinoid tumours of the rectum

Clinical study

PESKIN and ORLOFF (1959) presented a study of 25 patients with carcinoid tumours of the rectum. Carcinoid tumours were shown in 1952 to secrete serotonin; meanwhile, serotonin was isolated from a malignant carcinoid. Concurrently, a malignant carcinoid syndrome was described. The lesion appears to originate in the Kulschitzky or argentaffin cells of the crypts of Lieberkühn. Extra-appendiceal tumours appear as one or more yellow or grey submucosal nodules, occasionally polypoid, ulcerating and constricting. Microscopically, they consist of nests or columns of small epithelial cells in a fibrous stroma, in rectal carcinoids often exhibiting "ribbon-like festoons" (Stout, 1942). One of every 15–20 gastro-intestinal carcinoids occurs in the rectal area, generally in middle or old age and in both sexes. In 17 patients, the chief symptoms were pain, bleeding and constipation; the remainder were asymptomatic. Weight loss, obstruction, diarrhoea and an abdominal mass were present in some cases. Carcinoids, contrary to earlier beliefs, have a high malignant potential, varying with their site of origin. Metastasizing and non-metastasizing growths cannot be differentiated by their histology. Microscopically, the majority appear benign but local extension into and beyond the muscular coat of the bowel and metastases in lymph nodes or other organs are suspect. In this series, malignancy occured in 40 per cent of the cases. Of 15 lesions, measuring under two centimetres in diameter, only one was malignant, while 9 of 10 with greater diameter demonstrated metastases or local extension. Size, then, constitutes a surgical indication. The syndrome accompanying cases with liver metastases includes episodic flushing, telangiectasia and cyanosis, chronic diarrhoea, dyspnoea and cardiac valvular disease. Although in six cases, extensive hepatic metastases developed, no patient suffered from the clinical phenomena of excessive serotonin. Three forms of treatment were employed: local excision, radical resection and palliative measures. Rectal biopsy revealed benign lesions in 15 cases successfully treated by local excision. Three of four patients treated by abdomino-perineal resection are well. The remaining six died from widespread neoplastic disease.

Serotonin and pulmonary thromboembolism

Experimental studies

SANDERS and his colleagues (1959) explored the relationship between the haemodynamics of experimental pulmonary embolism and serotonin in the dog. This animal resembles man in its responses to serotonin and in the changes in serotonin metabolism produced by drugs. By studying the haemodynamic aspects and the serotonin content of blood and lung in dogs, cats and humans, the authors hoped to follow the possible role of serotonin in pulmonary thromboembolism. In Group 1 (25 dogs) a segment of external jugular vein was isolated following the administration of homologous serum. The resulting clot was released either intact or as a "shower" of small emboli while pressures were recorded in the pulmonary artery. In Group 2 (25 dogs) serotin was injected intravenously. For comparison, similar injections were made into the left atrium and the aorta and pressure tracings recorded. In Group 3 (30 dogs) one or more lobar arteries were obstructed. Extensive occlusion resulted in definite pulmonary hypertension with a transient fall in systemic pressure. The serotonin content of whole blood serum and clot was also determined in human subjects and in normal cats and dogs as well as the serotonin concentration in the lungs of these subjects. The serotonin content of cat blood was

PROGRESS IN FRACTURE SURGERY

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INTRODUCTION

There have been many notable developments in the management of injuries during the twelve years since the original chapter on fractures in *British Surgical Practice* was written (Holdsworth, 1948). To Charnley (1950) goes the credit of a more convincing explanation of bone healing. His principles are easily understood and originate from his observations on bone behaviour in Key's (1932) method of compression arthrodesis of the knee (solid bony union in four weeks was the remarkable basic finding). He found that cancellous bone does not throw out callus (to any extent) and when in close contact with more cancellous bone unites rapidly. Callus is a feature of fractures of long bones and is generated only in periosteum and endosteum. In fractures involving cancellous bone there is no death of osteocytes, because of good blood supply. On the other hand, cortical bone osteocytes at fracture level are starved of blood supply and are rendered incapable of osteogenesis. An understanding of these principles makes recent developments in treatment more comprehensible.

Intramedullary nailing for fractures of long bones has been widely and enthusiastically adopted, but there are now signs of a swing away from indiscriminate nailing, because of some disastrous complications and the indications are becoming more clearly defined, for example, certain femoral fractures in adults, pathological fractures of long bones, and in the treatment of non-union of long-bone fractures in conjunction with cancellous bone grafting. Although tibial nailing has found favour with some, it has been discarded by such authorities as Böhler and Ehalt (1958).

More operative reductions of all types have been performed, but the increase in resistant hospital infections in the last few years has led many surgeons to revise their indications for operative intervention. It is certainly not justifiable to convert a simple fracture into a compound one simply to cut short the hospital stay. The timing of operative treatment (internal fixation) has been reconsidered by thoughtful surgeons. Until recently, it was felt that early operation was advisable because there was less interference with the normal healing process and, of course, the earlier the operation the easier was exposure and structure identification and reduction of the deformity. There is a growing body of opinion that delayed operation (from 10 to 20 days) is followed by a much greater success rate in union of the fracture. The reason for this is to be found in the rapid improvement in soft tissue

diagnosis and treatment are the most important points in these cases, and they also show that prostigmine treatment, which should be begun immediately post-operatively, and the systemic use of modern antibiotics, are of great importance. The authors recommend that an ordinary duodenal tube should be used instead of a Miller-Abbott tube for pre-operative aspiration of the stomach and the upper part of the small bowel, as it is easier to use and causes less discomfort.

Surgical treatment of cancer

Prophylactic and adjuvant use of nitrogen mustard

The prophylactic and adjuvant use of nitrogen mustard in the surgical treatment of cancer is discussed by MRAZEK and his colleagues (1959). The effect of nitrogen mustard is being investigated in the hope of destroying cancer cells which are liberated into the blood stream at the time of operation or shortly before operation, and are beyond the scope of surgical resection. A study has been made of 136 cases of cancer of the breast, colon and rectum, of whom one-half received nitrogen mustard immediately after surgery and the other half were controls. To minimize the danger of drug toxicity, and to make the series more valid with a small number of cases, patients over 70 years were excluded from the study. Cases with multiple primary tumours, or a previous history of cancer, those in whom it was felt that a curative resection had not been accomplished, and cases of inflammatory cancer of the breast were also excluded. The total dose (per course) of nitrogen mustard was 0·4 milligram per kilogram of body weight; to minimize the danger of overdosage in obese patients, the maximum dose is limited to 30 milligrams. Antibiotics are given as a routine for several days; blood counts are taken post-operatively, with particular attention to the white blood cell and platelet counts and haemoglobin level. In the first follow-up year nitrogen mustard is given, at intervals of four months, to all patients whose white blood counts are above 5,000 cells per cubic millimetre; bone marrow depression, however, becomes more severe after each dose of nitrogen mustard, and of 30 patients treated over one year previously only 23 received a second course. The treatment caused bone marrow depression and leucopenia in most of the cases and especially in the obese patients; the leucopenia responded to transfusion and the treated patients required a considerably larger transfusion post-operatively. Other complications, such as wound infection and pneumonia, were not increased in frequency, but in some cases may have been increased in severity; post-operative complications and leucopenia were not correlated. There were no post-operative deaths directly attributable to nitrogen mustard administration and the operative mortality rate was the same in the two groups. There have so far been five recurrences and one death from cancer in the treated breast cancer patients compared to 12 recurrences and seven deaths in their controls. The recurrences in the colon-rectal group have so far been too few for comparison.

REFERENCES

Bean, W. B., and Funk, D. (1959). *Arch. intern. Med.*, **103**, 189.
Hoyer, A. J., and Solheim, K. (1959). *Surg. Gynec. Obstet.*, **109**, 555.
McCrea, J. M., and Conn, J. H. (1959). *Surgery*, **46**, 902.
Mrazek, R., Economou, S., McDonald, G. O., Slaughter, D. P., and Cole, W. H. (1959). *Ann. Surg.*, **150**, 745.
Peskin, G. W., and Orloff, M. J. (1959). *Surg. Gynec. Obstet.*, **109**, 673.
Pollock, A. V. (1959). *Brit. J. Surg.*, **46**, 543.
Rond, P. C. (1959). *Surgery*, **45**, 729.
Sanders, R., Waalkes, T. P., Gilbert, J. W., and Terry, L. L. (1959). *Surg. Gynec. Obstet.*, **109**, 455.
Sandler, M., Davies, A., and Rimington, C. (1959). *Lancet*, **2**, 318.
Stout, A. P. (1942). *Amer. J. Path.*, **18**, 993.
Thorson, Å. H., and Nordenfelt, O. (1959). *Brit. Heart J.*, **21**, 243.
Wilson, H., and Butterick, O. D. Jnr. (1959). *Ann. Surg.*, **149**, 641.

However, it has been repeatedly pointed out that full, normal, painless function is almost invariably the result even when the joint remains dislocated and operative fixation is seldom indicated, except on cosmetic grounds.

FRACTURES OF THE UPPER END OF THE HUMERUS

There has been considerable change recently in the treatment of fractures of the upper end of the humerus for four main reasons.

(1) There is widespread dissatisfaction with the abduction splint. It is uncomfortable, tends to slip and if inefficient and not accompanied by traction may allow the fracture position to deteriorate, and has proved on many occasions to be dangerous. It certainly prevents functional activities.

(2) The weight of the arm (15–18 pounds) suspended by a collar and cuff sling (Fig. 23) provides sufficient traction in the position of rest (arm by the side) to maintain reduction of a grossly displaced fracture, and to improve the position of a fracture that is not sufficiently displaced to require manipulation. The use of a sling is contra-indicated, because it is possible to reduce the gravity pull to nil by a tight sling, or even to angulate the fracture. Traction by the weight of the arm through a collar and cuff can be maintained at night by propping up the patient with a bolster into the semi-upright position.

(3) *Treatment by a collar and cuff sling allows gravity assisted exercises at the* elbow and shoulder to be carried out after the third day with a marked improvement in the range of movement at the end of treatment (Figs. 24, 25).

(4) When a person in a collar and cuff sling is taught to bring out the hand through an opening in the clothes this hand can be used for many functions, for example, holding, assembling (Fig. 26), knitting, sewing and so forth. If the surgeon will palpate the shoulder while the patient is using the hand in this way he will find that the shoulder muscles are active, although the joint itself is nearly stationary. The constant use of the hand at selected work maintains good shoulder muscle tone while the arm is kept in the collar and cuff next to skin. It is obviously easier for good muscles to move the shoulder when freed from the side than for wasted muscles to try to move a stiff shoulder.

Impacted fractures

In impacted fractures a clinical diagnosis may be difficult because a certain range of active movement without pain is possible. In an older person a severe deformity is acceptable in the presence of impaction. Treatment is by a collar and cuff and gravity assisted movements from the third day. It is not necessary for such a patient to sleep in the upright position. The collar and cuff can be discarded in the fifth week and antigravity exercises started. In teenagers it is necessary to reduce considerable displacement by manipulation under anaesthesia, and the rest of the treatment is as for unstable fractures.

Unstable fractures of the neck of humerus

The diagnosis in unstable fractures of the neck of the humerus is simple because of the characteristic swelling in this region and the pain which accompanies any attempt at active or passive movement and the absence of pain on gravity assisted

circulation, particularly in the damaged periosteum, that takes place in the week or two following injury. The trauma of operation, added to the injury, without this period of recovery may be sufficient seriously to devitalize portions of the all important periosteum.

The shoulder spica has virtually disappeared (except for the after treatment of posterior dislocation of the shoulder). Changes in the attitude towards spinal fractures have excited considerable controversy and the indication for different methods of treatment are becoming clearer.

But the most important developments have been in the social and industrial aspects of injury, that is, the consideration of the patient as a person and not merely the treatment of his fracture. Individual arrangements for an early return to full daily living, by contact with industry about selected and modified work, and setting up Rehabilitation Centres for solving difficult problems, have become routine in many Fracture Clinics in the United Kingdom. This concept of normal living and work as an integral part of therapy has led to adaptations and alterations in accepted principles of splinting, that is, the provision of hinges at the elbow in certain fractures about the wrist with prevention of temporary disability and reduction in the final disability.

There is more awareness of the psychological damage by the careless use of terms, which convey to the lay mind inevitable crippledom. It is clearly the duty of each surgeon, who uses the term "broken back" or "fractured spine", to explain with emphasis that a complete recovery is possible (in 70 per cent of instances) and probable if the patient becomes a willing and enthusiastic partner in the recovery programme. Similarly, the term "head injury" does not convey to most people the spectre of persisting disability, but the diagnosis "fractured skull" conjures up the vision of permanent invalidism in the minds of many and, furthermore, is an inefficient clinical label.

ACROMIO-CLAVICULAR DISLOCATION

The deformity of the shoulder in an acromio-clavicular dislocation is more likely to be spotted clinically than radiologically, because most x-rays are taken with the patient lying on the examination table. To demonstrate the deformity radiologically antero-posterior films are taken with the patient both lying and standing.

Reduction and fixation

Because redisplacement frequently occurs following reduction and fixation of the shoulder by the Robert Jones' method of strapping, many methods of more stable fixation have been developed. The best method is internal fixation across the joint. The acromio-clavicular joint and coracoid process are exposed from in front, the dislocation is reduced and stabilized by drilling a Kirschner wire through the acromion across the joint and into the clavicle, the acromio-clavicular capsule is then repaired and the conoid and trapezoid ligaments sutured. After operation gravity assisted movements are started on the following day—a sling is worn for two weeks when selected or modified activities are encouraged. The Kirschner wire can be removed at the end of six weeks. Another method of internal fixation is by inserting a screw through the coracoid process into the clavicle.



FIG. 25.—Abduction by gravity pull can be obtained to 90 degrees by posture.



FIG. 26.—Simple assembly jobs are helpful in maintaining the tone of all the shoulder muscles without movement of the joint itself.

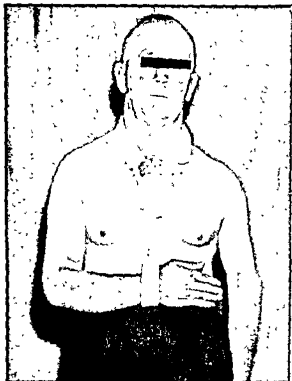


Fig. 23.—Collar and cuff sling next to skin used for injuries around the shoulder joint.



Fig. 24.—Gravity movements of elbow and shoulder can be used after the third day



FIG. 27.—Most occupations are possible with a plaster from axilla to wrist which allows full wrist function.

deformity. The posterior displacement is then corrected as the elbow is flexed in the classical manner. In the correction of late varus, or "gunstock" deformity, a simple wedge osteotomy is not sufficient by itself and guide wires are necessary to ensure correction of rotation.

It must be emphasized that the supracondylar fracture of the humerus in children has an imposing list of possible complications, one of which (Volkmann's contracture) is particularly serious.

Other complications include persisting stiffness (myositis ossificans), nerve injury, particularly the median nerve, and late "gunstock" deformity.

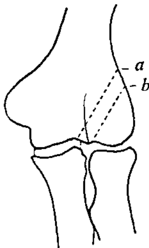


FIG. 28.—The fracture through the line *b* is stable when reduced. The fracture through the line *a* is unstable and requires pin fixation.

movement. Treatment is identical to that for impacted fractures, except that the patient must sleep in the semi-sitting position for the first few weeks, and union takes from one to two weeks longer, depending on the age of the patient.

Fractures of the greater tuberosity

Fractures of the greater tuberosity may occur alone, or may complicate other fractures or dislocations. If not displaced, an outside sling for a few days, together with exercises is the only treatment necessary. If appreciably displaced open reduction and internal fixation is indicated, after which the programme for impacted fractures is followed.

Fracture dislocations of the shoulder

There are two main types of fracture dislocation of the shoulder; in the first and more common injury, the greater tuberosity is torn off. The dislocation can be readily reduced under relaxation anaesthesia by gentle traction on the flexed forearm with one hand, while the other hand surrounds the head in the axilla and lifts it into place. The after treatment is the same as that for a dislocated shoulder.

In the second type, the head is separated from the shaft and lies outside the joint. It is a most unrewarding injury to treat. Sometimes gentle manipulation is successful, but more often it is not. In these cases, repeated manipulations are unwise, and open reduction with mechanical fixation of the head on the shaft may be necessary. The complications are numerous and the prospect of good movement is poor in the majority of cases.

INJURIES IN THE REGION OF THE ELBOW JOINT

In general, most injuries around the elbow joint can be treated in plaster which extends from the axilla to the wrist (Fig. 27)—namely undisplaced fractures, fractures of the head of radius and neck of radius with minimal displacement, and other fractures that have been stabilized by operative treatment. Plaster splints should not be completed until the swelling has subsided (at about 5–7 days), and should be lined by a generous cuff of felt at each end. This type of splintage allows full use of the shoulder, wrist and hand, and twisting movements of the forearm, and permits a return to near normal function. It must not replace the collar and cuff sling for those conditions that require moderate flexion of the elbow to maintain position of a replaced fragment, for example supracondylar fracture and fracture of the external condyle.

Supracondylar fracture

It is now more generally recognized that there is frequently a rotational element in the deformity accompanying supracondylar fractures. This rotation should be corrected to prevent troublesome varus. The classical manoeuvre in reducing the deformity of a supracondylar fracture is altered slightly as follows: traction is applied in the time-honoured way but with the forearm pronated and with the elbow slightly flexed. While traction is still being applied the lateral shift is corrected and the lower fragment rotated outwards to correct this important element in the

digital pressure over the head of radius. Should this procedure not result in good position, replacement by operation is indicated. Excision of the head of the radius is contra-indicated in children.

COLLES'S FRACTURE

All surgeons agree that a certain amount of recurrence of deformity takes place after reduction of a Colles's fracture and plaster fixation. Often, in spite of considerable deformity, function remains good. Sometimes, however, pain and stiffness and loss of function accompany this recurrence of deformity. For this reason many attempts have been made to maintain reduction. The most important contribution to this end has been the ulnar deviation position. If after reduction (*see British Surgical Practice*, Vol. 4, p. 193) the hand is deviated ulna-wards as far as it will go while the plaster is setting, the amount of slip during the first few weeks will be reduced considerably. This position still allows use of the hand for most daily purposes and for many types of occupation. The position can be further improved by taking the plaster above the elbow and fixing the forearm in pronation. This method, however, interferes so much with the function of the hand that it is seldom justifiable. The same effect can be obtained by hinging the plaster at the elbow, with the advantage that movement at the elbow permits near-normal use of the hand while maintaining pronation (Fig. 29).



FIG. 29.—A typist with a Colles's fracture reduced and fixed in pronation with an elbow hinge can regain her full typing speed within ten days of injury.

Separation of the capitellum

Separation of the capitellum (fracture of the external condyle) usually occurs in children under the age of five years and is more commonly followed by non-union and distortion of the elbow joint than formerly realized. For unstable fractures with delayed union, operative fixation can be effective. If allowed to persist, a cubitus valgus deformity develops with pain and stiffness in the elbow and possibly late onset ulnar palsy. A troublesome cubitus valgus can be improved by osteotomy, and a tardy ulnar neuritis requires operative transposition of the ulnar nerve to the front of the elbow, but the joint itself remains a source of pain and stiffness and weakness.

Fracture of the external condyle of the humerus occasionally occurs in adults. It is important to recognize the instability which is always present when the condylar fragment includes the radial ridge of the trochlea (Fig. 28). Such a fracture requires open reduction and fixation to prevent persistent lateral subluxation of the joint.

Pulled elbow

Pulled elbow (subluxation of the head of the radius) is the commonest disabling joint injury in childhood, occurring in children under the age of five years. In fact, it occurs more frequently than fracture of the clavicle. The story is typical, an adult holding a child's hand, lifts the child to prevent it falling after tripping. There is immediate pain and the hand hangs limply by the side. By careful examination full flexion, extension and pronation can be obtained, but there is a painful block to supination. Radiological examination does not show any abnormality. Sudden full supination with the elbow flexed at right angles is accompanied by a palpable click and the condition is cured.

Fracture of the head and neck of radius

Fissure fractures of the head of the radius are common and can be disabling if treated by the classical collar and cuff sling. If the haemarthrosis is tense it should be aspirated. The arm is then put in plaster from the axilla to the wrist with felt cuffing at the lower end of the plaster at the wrist. The individual is then encouraged to return to full daily living. This type of splinting allows the gradual recovery of pronation supination movements with normal activities and, as a rule, such movements are fully restored when the plaster is removed in from three to four weeks. Flexion extension recovery occurs naturally with normal use.

Marginal fractures, if depressed and impacted, may be treated in the same manner as fissure fractures. If the fragment is loose in the joint it should be removed and the further treatment follows the routine for simple fractures.

Comminuted fractures of the head of the radius are best treated by excision of the head and neck of the radius. These fractures are often accompanied by damage to the rest of the elbow joint and the surgeon should warn the patient that there may be some permanent restriction of movement.

Fractures through the neck of the radius in children with tilting of the head may sometimes be replaced by manipulation of the extended elbow into adduction and

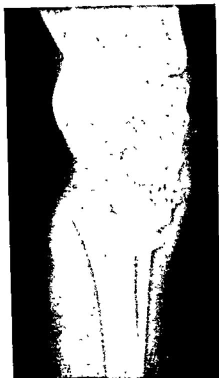


FIG. 31.—Fracture separation of the lower radial epiphysis.

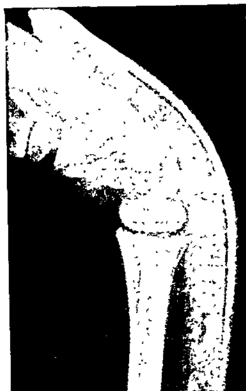


FIG. 32.—Reduction of fracture separation of lower radial epiphysis is stable in flexion.

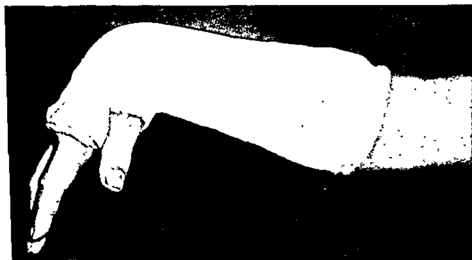


FIG. 33.—The position of full flexion of the wrist is necessary for the first two weeks.

Other developments are less attractive. Skeletal traction through the first metacarpal prevents the patient returning to any kind of selected or modified work and has a risk of thumb stiffness as well as considerable post-splinting wrist disability. Multiple transfixion pins and nails are cumbersome, interfere with function of the hand and introduce the added hazard of infection.

Complications

There are four chief complications of Colles's fracture as follows:

(1) Rupture of the extensor pollicis longus occurs several weeks after the injury and the patient complains of painless dropping of the distal phalanx of the thumb. Repair by transfer of the extensor indicis is a reliable procedure.

(2) Mal-union (*see British Surgical Practice*, Vol. 4).

(3) Disuse atrophy: if patients are persuaded to return to normal activities with some selection and modification within a matter of days, there will be no need for heat or massage or specially designed exercises at any stage. Frozen shoulders and stiff, weak wrists do not occur.

(4) Sudeck's atrophy occurs as often as once in two thousand injuries of all types seen in an accident service, and requires special attention (Plewes, 1956).

SMITH'S FRACTURE

Smith's fracture used to be the most dreaded injury of the wrist, because of the almost invariable poor result following adequate reduction and forearm plaster splinting. The problem was partly solved when it was realized that fixation in full supination was necessary to maintain position. This was accomplished by

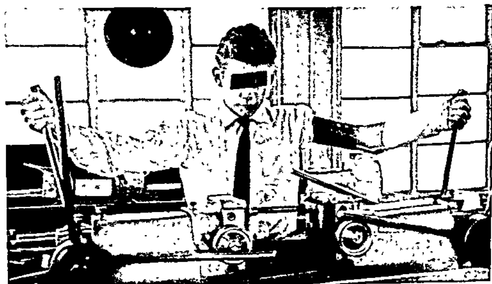


Fig. 30.—A young engineer returned to machine operating (horizontal drill) four days after reduction of Smith's fracture immobilized in supination by plaster elbow hinge and arm corset.

discarding the hyperextension plaster method of Watson-Jones (1955) was the high rate of recurrence of deformity after removal of the plaster. It was further argued that perfect function was compatible with persistent deformity and a wedge-shaped body in itself did not cause persistent pain.



FIG. 34.—Bennett's fracture dislocation of the first carpometacarpal joint with the classical displacement.



FIG. 35.—Open reduction of Bennett's fracture and fixation by transfixion with Kirschner wire, including the shaft of the first metacarpal, the small articular fragment and the adjacent metacarpals.

Some of these observations have not been substantiated. For instance, at the Massachusetts General Hospital in 1958, the correction of deformity was found to be maintained in 24 out of 26 patients followed for several years. Furthermore, it is well known that if some lateral tilting to the wedge deformity is left uncorrected, persistent root pain may be troublesome.

The present view may be summed up as follows: stable fractures, that is, simple wedge deformity without displacement of lateral articulations or rupture of interspinous ligament, can be treated either by reduction of deformity and plaster

incorporating the elbow in plaster with the forearm fully supinated. The next logical step was to apply a hinge so that elbow movements were possible while supination was maintained. Patients fitted with this equipment can return to modified or selected work within a few days of injury (Fig. 30). Recurrence of the deformity is now exceptional.

As in the procedure for Colles's fractures, full ulnar deviation after reduction of the deformity is an essential step in every case.

None of these patients need see the inside of a physiotherapy department if the surgeon will take the trouble to arrange for selected or modified employment to start within a few days of the injury.

FRACTURE SEPARATION OF THE LOWER RADIAL EPIPHYSIS

Complete reduction of the displacement is always possible by digital pressure and flexion of the wrist, but the epiphysis slips dorsal-wards to a certain extent within a few days unless the wrist is kept in full flexion in plaster (Figs. 31, 32). It is only necessary to keep this position for the first two weeks (Fig. 33), when the plaster is changed to the neutral position for a further two weeks.

BENNETT'S FRACTURE

There has been widespread dissatisfaction with the results obtained in Bennett's fracture by conservative means and by traction. Some fractures are stable with the thumb held in plaster with full extension at the carpo-metacarpal joint. When this is not so, stabilization by operation is indicated.

There are three satisfactory methods. In the first, a small screw is used to fix the small fragment to the shaft—a technically difficult procedure (Badger, 1956). In the second, a Kirschner wire is used to stabilize the position (Figs. 34, 35), the wire being removed four weeks later. The third method is just as satisfactory, and does not require any further procedure: the fracture dislocation is reduced under direct vision at open operation and fixed in position by an encircling stainless steel wire (Kerr, 1959). A full functional result can be expected from any of these three procedures.

FRACTURES OF THE SPINE

During the past ten years there has been considerable change in the treatment of compression fractures of the spine, a group comprising 65 per cent of all significant spinal injuries in the accident centres of Britain. This followed the work of Nicoll (1949). He found the results of reduction of deformity by hyperextension and plaster fixation were inferior to treatment by bed rest and exercises. The routine he recommended was rest in bed with immediate institution of an exercise programme, which progressed in vigour as pain subsided. Bed rest was usually required for from three to four weeks and was followed by a full day's programme of activity as an out-patient. With this method, he found a considerable increase in the number of injured miners who were able to return to the coal face. One of his reasons for

necessary in the first method. In the second, the period in hospital will vary from one to four weeks.

Severe crush, stable fractures in persons aged under 50 years should always be reduced.

Stable wedge fractures with some lateral tilt in the deformity, and with lateral root pain should be treated by adequate reduction in an attempt to relieve pressure and allow recovery of the affected nerve root.

Stable fractures above the eleventh thoracic body cannot be reduced because of the attached skeletal structures and, therefore, the alternatives for treatment are either plaster fixation in the normal erect posture (Fig. 38) with minimal stay in hospital, or bed rest and mobilization with a slightly longer stay in hospital.

Patients in the later middle-age group and older do not tolerate adequate correction or plaster fixation very well, and in these circumstances the bed rest and mobilization regimen is indicated.

Unstable fractures require much more careful consideration and assessment. Usually, the interspinous ligament is torn and there is a gap palpable between the two spinous processes. There is also considerable soft-tissue damage, especially to the intervertebral discs. If it can be shown clearly that the lateral articulations are in normal relationship and there is no cord damage, reduction of the deformity by hyperextension and plaster fixation is indicated. Otherwise, unstable fractures should be treated by operative fixation, particularly the ones characterized by rotational deformity and symptoms and signs of minor cord damage.

Patients with paraplegia require the very highly specialized treatment that can only be provided in a special unit.

FRACTURES OF THE CALCANEUM

The treatment of fractures of the calcaneum is still not satisfactory, and although steady progress has been accomplished in the past twelve years, there is still acknowledged to be a 20 per cent permanent disability in severe injuries.

With more adequate walking appliances coming into use (below-knee plaster with metal reinforcement at the ankle, and an adequate overboot, Fig. 39), better leg function is possible and a return to near-normal activities is encouraged after the initial treatment.

Fractures without joint involvement

Fractures without joint involvement are treated by elevation of the leg until the swelling has subsided. Early manual reduction of displacement of a large fragment is usually satisfactory. A walking plaster can be applied in from seven to ten days and unrestricted activities allowed within the next week. These patients can return to selected ground level work at this time and have the plaster removed in six weeks although a supporting bandage will be required for several weeks more. The same programme is recommended for the patient with a fracture separation of the tuberosity replaced by operation or manipulation, or with isolated fracture of the sustentaculum tali or anterior end of the calcaneum.

fixation (Watson-Jones's method, Fig. 36) with exercises and return to selected or modified work within two weeks of injury (Fig. 37) or by Nicoll's method and return to work in six weeks or more. In either case, the final result should be perfect if rehabilitation services are adequate. No more than three days in hospital is

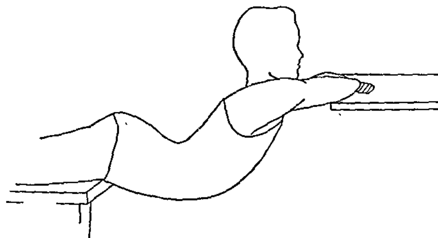


FIG. 36.—The two-table method of hyperextension described by Watson-Jones. The plaster jacket extends from the sternal notch to the pubis.



FIG. 37.—One week after reduction of a wedged first lumbar body by Watson-Jones's method. This man is on selected work—bar bending.



FIG. 38.—Plaster jacket with normal posture for fractures of the thoracic spine above T.11.

patient is anaesthetized and the spike is inserted into the long axis of the tongue fragment and checked by x-rays. With the patient lying prone and the knee flexed, the limb is lifted just off the table by the spike and the surgeon's hand placed just in front of the ankle (Fig. 41). The heel is then compressed manually from side to side and a plaster slipper applied over thin padding to maintain the position of the spike in relation to the heel. This plaster does not interfere with movements of the ankle or subtaloid joint, and the aim is to restore movements in both of these joints in a matter of days. The patient is allowed up on crutches in two weeks. The spike and plaster are removed in four weeks and a walking plaster applied and kept on for a further four weeks.



FIG. 40.—The tongue-type of fracture with displacement of the lateral half of the posterior subtaloid joint.

If this procedure is not successful in accurate realignment of the subtaloid joint it should be abandoned, the spike removed and the simple exercise routine started immediately. It is not a method to be used in patients over the age of 50 years, and it should be noted that too much force with the use of the spike may result in overcorrection. The method is more likely to be successful when the plantar surface of the calcaneum is intact.



FIG. 41.—Essex-Lopresti's method of transfixion of the tongue fragment with a Gissane spike and reduction by lifting the leg off the table with the spike and with the other hand in front of the ankle.

Joint depression-type

A large fragment, including part of the subtaloid joint depressed into the body of the calcaneum (Fig. 42), can be elevated by direct exposure on the lateral side and maintained in position by a long Gissane spike. This is followed by the Essex-Lopresti plaster slipper and exercise routine. Alternatively, a cancellous graft taken from the iliac crest can be used to maintain the position of the replaced joint

Comminuted fractures with minimal joint injury

It is now widely believed that comminuted fractures with minimal joint injury can be treated conservatively with better results than have been obtained in the past by skeletal traction and immobilization. The leg is elevated and the soft-tissue haematoma is infiltrated with procaine and hyalase. Active exercises for the ankle are started immediately and for the subtaloid joint as soon as pain has gone. Weight bearing is allowed in a supporting bandage when tenderness and swelling have subsided. These patients can manage selected and modified work in 12–15 weeks.



FIG. 39.—This below knee plaster is skin tight with the ankle exactly at right angles. The overshoe is waterproof and lined with sorbo rubber. There is a piece of sprung steel inserted between the layers of the sole to help in developing a normal heel-toe gait.

Fractures with disorganization the of subtaloid joint

Tongue-type

A large fragment consisting of the tuberosity and outer half of the posterior subtaloid joint (the so-called tongue-type) (Fig. 40) can be manipulated into position by using a Gissane spike (1947) as shown by Essex-Lopresti (1952). The

Advantages

The great advantage of the intramedullary nail is the excellent fixation achieved by its proper use. No additional form of external splinting is necessary. Early ambulation and unrestricted knee movements are possible. Since there is no need to disturb the periosteum at the fracture site, the method need not delay union. Moreover, in the treatment of non-union of long bone fractures, the use of an adequate nail and cancellous bone grafts has proved to be a decided improvement over all other methods.

Indications

Ten to fifteen years ago nailing was used indiscriminately for all long bone fractures as a method of treatment which was supposed to give quicker and better results than other procedures. This enthusiasm was soon damped down by reports of dreadful complications. At the present time the main indications for the use of an intramedullary nail are:

(1) The transverse fracture of the femur, which occurs at least five inches above the knee and two inches below the lesser trochanter, when conservative methods have not been successful.

(2) Fractures of long bones in their middle two-thirds, that cannot be treated adequately by conservative means, because of other associated injuries (head injury, spinal injury, chest or abdominal injuries, multiple other fractures and joint injuries).

(3) As a means of internal fixation when cancellous bone grafting for non-union is required.

(4) In pathological fractures of long bones intramedullary nailing is becoming increasingly accepted as the method of choice, not only because of the ease of nursing after operation and the increased comfort to the patient, but because of the nature of the disease increased risks are justifiable, and the other methods of internal fixation are inadequate.

The most common situations that call for nailing are fractures of the proximal half of the femur, fractures of the ulna (unstable Monteggia fracture-dislocations) and non-union of the mid-humerus.

Requirements

No surgeon should use intramedullary nailing without being fully aware of the possible complications, without an accurate knowledge of his routine operative infection rate, and without special equipment.

Principles for the femoral nail

The following principles for the use of the femoral nail are to be noted.

(1) The more adequate the filling of the medullary canal, the more rigid is the fixation. Usually, *there is an area of narrowing of the medullary cavity of the femur* at the junction of the middle and upper thirds. A nail that will go past this obstruction will not fit snugly throughout the rest of its course. For this reason many surgeons prefer to ream out the canal before introducing the nail. Küntscher uses a reamer for every nailing operation. This is one certain way of preventing nail

surface and to fill the gap beneath it. In the latter case, a full below-knee plaster must be used and replaced by a walking plaster in two weeks.

Comminuted fractures with displacement

Subtaloid arthrodesis is still the method of choice for severe comminuted fractures with displacement of joint surfaces or for deformities mentioned above that cannot be reduced adequately, and for the foot that remains painful after any form of treatment. It is wise to reduce gross deformity by manipulation and to delay operation for several weeks. A walking plaster can be applied a few weeks later with the heel in neutral position, taking care to avoid any trace of varus, and with the use of a suitable overshoe a return to full function is encouraged.



FIG. 42.—A large fragment containing a considerable portion of the subtaloid joint can be elevated into position by open operation.

INTRAMEDULLARY NAIL

History

Intramedullary nailing of fractures has become established in many centres and the indications and complications of the method have steadily become more clearly defined over the past twelve years. Although McLaysen in 1897, Delbet in 1906, Lambotte in 1907 and Schöne in 1913 described intramedullary nailing as a method of treatment for fractures, it was Hey Groves in 1916 who first introduced intramedullary fixation with massive nails for fractures of long bones, and his method of retrograde nailing is the one most widely used today. Surgical use of nails from 1920 on, however, fell into disrepute, because of the amount of tissue reaction they produced. Following the introduction of high quality stainless steel, Joly and Davies in 1937 and Lambrinudi in 1940 revived interest in the method, and it became popular in the Finnish war of 1942, mainly as a means of treatment which allowed early evacuation of these patients from hospital. Böhler adopted the method during World War II when Küntscher (1940) described his specially designed nail. Küntscher's method differed from Hey Groves's in three ways. The nail was hollow, it was introduced at the end of the long bone, and the medullary cavity was mechanically reamed to ensure accurate fit throughout the whole length of the bone.

Since the end of the war the method has spread to all parts of the world and although some surgeons have been so impressed with the serious nature of the complications that they condemn the method outright, in the majority of accident clinics it has found its proper place as the treatment of choice in certain situations in adults.

FIG. 43.—This bone abscess first produced symptoms eight months after the original nailing operation.



FIG. 44.—In this case the nail was removed because of infection. There are two abscesses with a sequestrum in each cavity.

impaction, which may result in either shattering the femur or necessitate the use of a hacksaw. The cloverleaf design introduced by Küntscher permits a slight flexibility and improves the snugness of the fit. Furthermore, bone absorption takes place where the nail presses on the walls of the medullary cavity and this slack can be taken up by a nail which can expand a little in its diameter. There is, therefore, less likelihood of such a nail migrating.

(2) *There is a correct size of nail for each femur. It should project proximally* far enough to allow easy removal, that is, the eye of the nail should be situated just beyond the cortex proximally. The nail should extend to the intercondyloid notch and no further. All this means careful pre-operative measurements.

(3) Care must be taken to avoid distraction at the fracture site.

(4) Experience shows that a delay of two or three weeks after injury, before nailing, is of advantage, that is, more rapid union and less risk of delayed union, unless for other reasons nailing is needed as an urgent measure.

Technique

There are *two main methods of inserting an intramedullary nail into the femur*— the blind and the open.

Blind method

Küntscher (1958) uses the blind technique, that is, he inserts the nail through the tip of the greater trochanter over a guide which has been demonstrated radiologically to be in the correct position. The fracture is not exposed, but is reduced and controlled under the fluoroscopic screen. *In every case, a reamer is used before* the actual insertion of the nail. There are two main advantages of this method; there is no disturbance of the periosteum at the fracture site and the risk of infection is less. However, it is technically more difficult than the open method and there is the risk of repeated exposure of the operator to x-rays. Furthermore, it is difficult to control rotation at the fracture site.

Open method

Most surgeons use the Hey Groves technique of retrograde nailing. With the exact size in nails already determined, the anaesthetized patient is placed on the sound side with the broken thigh flexed at the hip and the knee. The fracture is exposed by a mid-lateral or postero-lateral incision to avoid damage to the quadriceps muscle. Any muscle interposed between bone ends is removed and care is taken not to disturb the periosteum. The nail is introduced into the proximal shaft and pushed proximally until it bulges the skin above the greater trochanter. An incision is made over the presenting end of the pin, the fracture reduced under direct vision and the nail driven down through the distal fragment to the predetermined position.

There are three main advantages of the open method: (1) no fluoroscopy is necessary; (2) direct vision makes reduction of the fracture simpler. In fact, the whole procedure is technically easier; and (3) the additional fracture (butterfly fragment), which is not detectable by radiography becomes visible.

The great disadvantage is the risk of disturbing the periosteum and the greater risk of infection.

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SELECTED ABSTRACTS

Fracture patterns

BUHR and COOKE (1959) refer to the tendency for old people to sustain minor forms of trauma, especially falls. Aetiological factors include general muscular weakness, arthritis of the joints of the lower limbs, paralysis agitans and lesions of the pyramidal tract. Falls may also occur during a syncopal attack or at the beginning of a febrile illness. The risk is increased in patients with vertigo, failing eyesight or defective hearing. A fall backwards is likely to be heavy, for the patient is unable to check the fall by using his arms. With reference to accidents in the home, it is recorded that in 28 per cent of cases the causes can

Post-operative management

The post-operative management includes exercises and active knee movements on the third day and controlled weight bearing as soon as the wound has healed. Although some advise crutches and no weight bearing, it has been pointed out that this may allow the weight of the leg to distract the fragments. Therefore, some



FIG. 45.—Infection in this case only became apparent six months after insertion of the nail. Infective erosion of the outer surface of the cortex is apparent.

weight bearing is allowed on the first day that the patient is out of bed. Unrestricted weight bearing is encouraged as soon as there is radiological evidence of union.

There is no need to remove an intramedullary nail that is not causing symptoms, because modern nails are made from metal that is inert and will not corrode.

Complications

It has been said that the use of intramedullary nailing, if applied to improperly selected cases, or inefficiently performed, offers more possibilities of trouble than

any other. Infection is the most dreaded complication (Figs. 43, 44, 45) and it is mainly because of this possibility that most surgeons prefer to delay the operation of nailing for some days and to use the method only when specifically indicated. Moreover, this problem of infection is not likely to diminish in the future. More and more hospital infections are due to resistant strains of staphylococci, and such an infection extending throughout the whole length of the femur can cause considerable and protracted anxiety for both surgeon and patient.

During the actual operation, the difficulties that occur include impaction of the nail (and sometimes this means using a hacksaw because the nail cannot be removed), splitting of the shaft as a result of forcing a nail through a marrow cavity too small for it, distraction of the fracture, and penetration of the distal cortex with consequent damage to vessels and nerves. Fat embolism has been reported by several authors and others have reported shock.

Late complications

Late complications are also encountered: delayed union, nail bending and nail migration. If the nail migrates proximally, a bursa may form in the soft tissues, or there may be acute discomfort. Migration distally into the knee joint is, fortunately, less common. If the nail bends it must be replaced by a new one slightly larger than the original. The bent nail can only be removed by first correcting the deformity.

REFERENCES

Badger, F. G. (1956). *J. Bone Jt Surg.*, 38B, 771.
Böhler, L., and Ehalt, W. (1958). *The Treatment of Fractures*, 13th German edition. New York and London; Grune and Stratton.
Cave, E. F. (1958). *Fractures and Other Injuries*. Chicago; Year Book Publishers.
Charnley, J. (1950). *Closed Treatment of Common Fractures*. Edinburgh; Livingstone.
Essex-Lopresti, P. (1952). *Brit. J. Surg.*, 39, 395.
Gissane, W. (1947). *J. Bone Jt. Surg.*, 29B, 254.
Holdsworth, F. W. (1948). In *British Surgical Practice*, Vol. 4, p. 165. London; Butterworth.
Kerr, P. (1959). Personal communication.
Key, J. A. (1932). *Sth. med. J.*, 25, 909.
Küntscher, G. B. G. (1940). *Arch. clin. Chir.*, 200, 443.
— (1958). *J. Bone Jt Surg.*, 39A, 702.
Nicoll, E. (1949). *J. Bone Jt Surg.*, 31B, 376.
— (1953). *Brit. med. J.*, 1, 879, 928.
Plewes, L. W. (1956). *J. Bone Jt Surg.*, 38B, 195.
Watson-Jones, R. W. (1955). *Fractures and Joint Injuries*. 4th ed. Vol. 2. Baltimore; Williams and Wilkins.

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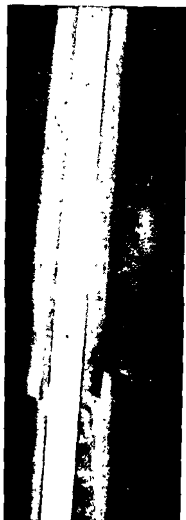


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management of fractures in elderly patients it is sometimes preferable to adopt open operation and internal fixation rather than conservative measures, for among patients in the older age groups long-continued splinting and rest in bed may considerably impair the health. Relative indications for surgical intervention include not only irreducible fractures but also those which are reducible but unstable. The term, relative indication, applies to any conditions in which the functional results are likely to be poor if surgery is not employed. These conditions include separation of the capitellar epiphyses in children and gross comminution of the head of the radius in adults. In cases of fracture-dislocation of the hip with separation of a fragment of the acetabulum the fragment should be restored to its correct position by means of vitallium screws. It may be necessary to remove intervening soft tissue such as the muscle tissue which sometimes becomes interposed between the bone fragments in cases of fractured femur. For the most part, operation should be performed on comminuted fractures only when the displaced fragments impede vital function. Surgical treatment of certain avulsion fractures should be directed towards restoration of the continuity of the vital musculo-tendinous mechanisms. If the line of fracture is parallel to the line of muscle pull the fracture becomes unstable. Treatment is by open reduction rather than placing the limb in an unphysiological position.

Prevention of venous thrombosis and pulmonary embolism

Trial of anticoagulant prophylaxis in fracture cases

Sevitt and Gallagher (1959) discuss the prevention of venous thromboses and pulmonary embolism in the injured. Those subjected to a controlled prophylactic trial of an anticoagulant were all over 55 years of age and with fractures of the hip; 150 received the anticoagulant and 150 did not. Careful laboratory control was found essential and repeated plasma-prothrombin estimations take time. Phenindione was the anticoagulant used and, as it is cheap, its use probably more than covers, in a financial sense, the cost of the extra laboratory work. It did not appear that the wounds of those operated bled more than under normal conditions. In the control series there were 43 cases of clinically recognizable thrombosis while in those under treatment only four had this complication. Unexplained unilateral swelling of a leg and unequivocal spontaneous pain or tenderness in the calf were diagnostic criteria. The main leg veins were examined throughout their length in any necropsies performed, as also were those of the abdomen. Of the controls the average stay in hospital of survivors with clinical thrombosis was 54·2 days, this being 15 days longer than the stay of control survivors without clinical thrombosis, while those given phenindione were about 12 days less in hospital if surviving. Evidently the drug saves much bed time. It did not appear that pulmonary embolism was always dramatic and immediately fatal. In about half the cases it was insidious and sometimes accompanied a marked fall of blood pressure resulting in acute renal failure. The two deaths from embolism in the phenindione series occurred after treatment was stopped and no patient had this complication while receiving the remedy. The writers provide an excellent diagram from which the extent of the various fatal thromboses may be seen at a glance. Post-operative haemorrhagic incidents were fairly common in the phenindione series and were treated by transfusion, stopping the drug or giving vitamin K. Major incidents were few. In some cases minor bleeding is unavoidable and need not cause anxiety. From the evidence of this trial it is concluded that phenindione might well be given more often, particularly in those aged over 50 years who are likely to have bed rest, for any reason, of more than a few days. This procedure might well reduce the deaths from embolism by four-fifths.

Supracondylar fractures of the humerus

Varus deformity of elbow

French (1959) states that when deformity occurs after supracondylar fracture of the humerus in children the gunstock or varus elbow is often encountered. The deformity is usually due to failure to correct rotational displacement of the distal fragment. So far as clinical examination is concerned, when the flexed elbow is used as a lever there is an

be traced to defective design or maintenance of the stairs, handrails, lighting, and so forth. Osteoporosis of old age is an important factor in the aetiology of fractures. Bone atrophy is increased by immobilization, malnutrition and endocrine abnormalities. The incidence of fractures among the aged could be reduced by improving the environmental conditions, encouraging mobilization and maintaining good nutrition. Endocrine therapy is indicated in selected cases. Oestrogen and androgen therapy exerts a bone-building effect and may be of value in the management of post-menopausal and senile osteoporosis of the spine. The authors present a statistical analysis of common fractures which were treated at the Radcliffe Infirmary, Oxford, during a period of five years. A study of the age and sex distributions showed that the graphs could be assigned to four classes, designated composite and A, J, L. These letters were employed because their shape resembled the patterns made by the curves of distribution. The composite group gave a bimodal pattern for which there was no obvious explanation, but the A group typified the wage-earners, for it showed a high incidence in male patients during the working period and a low incidence in youth and old age. A high incidence in young males and females gave the letter L pattern of pre-wage earners, and a pronounced increase in both sexes in old age, especially in females, gave the letter J pattern of post-wage earners.

Multiple fractures

Systemic changes and early treatment

Discussing systemic changes in patients with multiple fractures, COLEMAN (1959) points out that an average blood loss of 1,800 millilitres may occur during the first 48 hours. Interstitial haemorrhage in closed fractures may be extensive, especially in the soft tissues surrounding the pelvis and femur. Renal dysfunction may be severe in the aged and in patients with gross damage to the soft tissues or pre-existing renal disease. Accurate charting of the input and output of fluid is of assistance in estimating the degree of dysfunction. Within 4–8 days excessive breakdown of the tissues may set up a negative nitrogen balance, and sometimes the stress of trauma causes temporary "traumatic diabetes." Hypercalciuria is of little consequence during the early stages, but renal lithiasis may develop after prolonged immobilization. Occasionally hypo-adrenalism occurs in patients who have had cortisone injections prior to the accident. With reference to the treatment of multiple fractures, effective splinting is required in order to minimize shock. All open wounds should be converted into clean closed wounds as soon as possible. Haemorrhage is controlled and sterile dressings are applied. Tracheostomy should be performed if the free exchange of air is found to be impeded. Demerol or codeine therapy is of value for assuaging pain, but owing to its miotic effect morphine may cause difficulties in the evaluation of head injuries. Immediate replacement with whole blood is required. Dextran or serum albumin may be employed when blood is not available. The amount of fluid required for transfusion is evaluated mainly by clinical examination. In this context blood-volume studies and white blood cell counts are also of assistance. Supportive treatment includes psychotherapy and the administration of antibiotics and tetanus toxoid. Among a series of 20 cases severe renal dysfunction developed in a patient suffering from extensive damage to the muscle and soft tissues. Death took place 20 days after the injury. So far as minor complications are concerned, pyelonephritis, transient albuminuria and "traumatic diabetes" were detected in three instances.

Open reduction of fractures

ROAF (1959) discusses the indications for open reduction of recent fractures. An open wound is an absolute indication for operative treatment. Another indication is gross pressure upon nerves or blood vessels if this cannot be relieved by closed means or if severe impairment of function is likely to ensue. For example, pressure is likely to occur in children with supracondylar fractures of the lower end of the humerus and in patients with fracture-dislocation of the tarso-metatarsal region of the foot. So far as arterial occlusion is concerned, exploration is required if gross ischaemic signs are present. Diminution of the peripheral pulse is not in itself an indication for open operation. In the

the technique was employed. As compared with the use of closed methods, adoption of the technique resulted in fewer instances of malunion. Furthermore, so far as the incidence of non-union was concerned, nail fixation yielded better results than those obtained with other methods of open reduction. Infection, bursa formation and other complications were sometimes encountered. With increased experience, however, complications were circumvented for the most part.

Fracture of the carpal scaphoid

Treatment with immobilization of the thumb

Wallensten, Cronestrand and Lugnegård (1959) describe the management of 62 cases of fracture of the carpal scaphoid. The series comprised 53 men and 9 women. An encircling plaster of Paris cast was employed within two months of the injury. Extending from a line just below the elbow joint to the metacarpal heads, the cast was continued as far as the distal interphalangeal joint of the thumb. Comparison with another series of cases revealed that immobilization of the thumb had reduced the average period for healing by 56 days. Delayed union had been prevented by immobilization of the abductor pollicis brevis and other short muscles of the thumb.

Fractures of the neck of the femur

Early weight bearing

Murley (1959) advocates early weight bearing in the post-operative management of fractured neck of the femur. Adoption of this procedure assists in maintaining morale and preventing osteoporosis. The author describes 41 patients whose average age was 74 years. Surgical treatment consisted in fixation of the bone with a trifin nail within 48 hours of admission to hospital. When the skin had healed and as soon as the pain due to the operation wound had subsided the patient was encouraged to use partial weight bearing with the aid of crutches. The patient reached this stage 10–19 days after the operation and usually returned home on crutches within 5–6 weeks. The average period of treatment in hospital was 50 days. Adverse weighting of this period was ascribed to several factors. For instance, secondary operation was required in 5 cases and some patients were admitted with hemiplegia. In a few instances the relatives failed to co-operate or the home conditions were considered unsuitable to warrant early discharge. Further observation revealed that union had taken place in 28 cases. Two patients died in hospital and 6 patients died at home. With regard to the survivors, unguarded weight bearing was usually allowed 3–6 months after the operation. This decision was made after clinical examination and studies of serial radiographs. Union was assumed to be present if there was no clinical evidence of displacement of the fractured bone.

Undisplaced fractures of femoral neck in children

Avascular necrosis

Durbin (1959) discusses avascular necrosis complicating undisplaced fractures of the neck of the femur in children. Any blood supply through the ligamentum teres in childhood is generally believed to be unimportant compared with that of the metaphyseal and epiphyseal branches of the posterior circumflex artery. Anastomotic branches from the diaphyseal vessels through the epiphyseal plate have been disregarded. Since, however, fracture of the femoral neck in children is near the base and well below the entrance of the epiphyseal vessels, damage to the diaphyseal vessels is likely, with potential avascular necrosis. Three cases are described. In the first, a boy of 7 years fell, injuring his left hip. Radiography revealed a fissured fracture of the trochanteric region of the femur without displacement. The hip was immobilized for three months; three months later he had full, painless movement. After five years he began to limp. Radiological examination showed avascular necrosis. The second case was a boy of 14 years sustaining a trochanteric fracture of the femur without displacement. After three months immobilization, full movement was regained. Six months later, pain in the hip developed and radiographs revealed

apparent increase in internal rotation of the shoulder. On radiological examination in the antero-posterior position the radiograph is likely to show that the supracondylar ridges on the upper fragment are unequal in length. In the lateral position the x-ray film reveals that the longer spike of the upper fragment points forwards. Reduction of the fracture is effected under radiographic control. With the elbow flexed and the forearm pronated traction is applied and the lateral shift of the distal fragment is corrected. Posterior angulation and rotation of the lower fragment are also corrected. The former deformity is abolished by pressing the thumb on the olecranon and increasing flexion of the elbow. Wedge osteotomy is performed in cases of long-standing deformity. The lower end of the humerus is approached through an incision in the triceps. After reflection of the muscle two drills and two screws are inserted to serve as guides. Then a triangular wedge of bone is excised with its base on the lateral supracondylar ridge. The cut surfaces are approximated by tightening a wire attached to the screws and rotational deformity is controlled by moving the screws into position.

Fractures of the forearm

Internal fixation

SMITH (1959) reports on a series of 112 cases of fracture of the shafts of the radius and ulna in adults. The series comprised 70 men and 32 women. In the majority of cases the injuries were due to traffic accidents and falls. Treatment consisted in open reduction and internal fixation. In 74 cases good or satisfactory fixation resulted from the use of metal plates and screws. Among the remaining cases non-union or slow union was observed in 22 instances, and the defect was most often encountered in patients aged 30–55 years. Usually union was relatively slow after severe injuries, in fractures of the mid-shaft and in fractures at the junction of the middle and lower thirds of the shafts. In several cases non-union was attributed to either a poorly applied plate or the use of a very small plate. Sometimes the plaster application was inadequate. The timing of the operation appeared to be a factor, for no cases of non-union occurred when the operation was performed after the sixth day. With delayed operation 50 of 52 fractures showed union within six months. It is believed that delay in operating allows time for the local circulation to become established. When the presence of non-union is suspected caution must be exercised before performing a second operation. For instance, at the end of the third month the radiograph may show a gap between the fractured bone ends, but subsequently this gap is often obliterated within a few weeks. Bone grafting is advisable, however, if the plate requires removal before radiological union is complete.

Medullary fixation

SAGE (1959) presents a detailed study of the medullary canal of the radius in the cadaver and describes the technique of medullary fixation of fractures of the ulna and radius. A straight triangular nail is employed in the treatment of diaphyseal fractures of the ulna. The elbow is flexed to an angle of 90 degrees and a nail is driven up the proximal fragment. When the nail reaches the posterior aspect of the olecranon an incision is made through the skin in this region and the nail is moved onwards until its distal end is at the site of the fracture. After reduction of the fracture under direct vision the nail is driven down the distal fragment. Provided the diameter of the medullary canal measures not less than three millimetres, use of a pre-bent triangular nail is indicated in all cases of diaphyseal fracture of the radius, apart from fractures of the proximal and distal fourths of the bone. A drill is inserted into the cortex of the radial styloid and directed towards the lateral epicondyle of the humerus. The point is advanced through a distance of 2–2½ inches. A nail is driven into the channel and the fracture is reduced. Radiological examination is performed in order to ascertain the final seating of the nail in the proximal fragment. For some forms of fragmentation of the bone additional fixation with wire loops may be required. Usually the nails are allowed to remain in place for one year, but their removal may be necessary before this period has elapsed if the formation of interstitial callus is delayed although the fracture site has been bridged by periosteal bone. The author reports on 50 cases in which

performed 11 years later, when the fragment and anterior cruciate ligament were removed. Eventually normal movement of the knee was achieved and the patient became free from symptoms.

Fractures of the shaft of the tibia

JACKSON and MACNAB (1959) report on 368 patients with simple or compound fractures of the shaft of the tibia. In 16 per cent of cases union was complete within 3 months of treatment and in 62 per cent of cases satisfactory union was achieved after a further period of 3 months. At the end of 18 months non-union was recorded in 2 per cent of the number of patients. The rate of union depended upon the degree of initial displacement and the extent of periosteal damage. In the management of most simple fractures treatment by means of closed reduction produced better results than those obtained from open reduction and internal metal fixation. On the other hand, spiral oblique fractures with moderate or pronounced displacement were more satisfactorily treated by means of screw fixation. With reference to the treatment of compound fractures, internal fixation tended to hasten union provided extensive dissection was not required. When plates were employed union was delayed and there was a pronounced increase in the incidence of complications such as osteomyelitis. The authors comment upon the efficacy of closed reduction and the hazards of extensive operations. If open reduction is required the decision to operate should be made within 14 days. Screw fixation affords minimal trauma to the soft tissues. Lottes's intramedullary nails, inserted by the blind technique, are of value in the management of unstable transverse fractures. Cortical wiring is best avoided. When extensive exposure of the fracture site is needed, internal fixation should be reinforced by onlay cancellous grafts. In view of experiments on bones it is considered that the periosteum acts as a barrier against fibrous-tissue infiltration of the site of the fracture. As for the relation between the injury and the type of fracture, when a steadily increasing force is applied at right angles to the long axis of the bone a transverse fracture results, but three times the force is required if the load is applied in a spiral fashion. Apparently the rate of union is influenced by the amount of soft-tissue damage and not by the age of the patient or the site of the fracture.

Supramalleolar fractures with associated subluxation

In their annual survey for 1960 a group of international surgeons discuss reconstruction procedures and WITT writes on supramalleolar fractures with associated subluxation. The injury usually follows a fall from a great height or a severe direct blow. Depending on the forces at work so may the foot be displaced in various directions and the author stresses that the severity of this displacement is of the greatest importance. This is not merely because of the bizarre position of the bones and bone fragments which results but particularly because of the associated injury to soft tissues. If the break is above the malleoli and open then all the conditions favouring infection are present and the local tissue changes may allow the whole foot to become the site of a haematoma. Not uncommonly the hard tissues damage the soft very severely though the skin is intact. If the bone adjacent to the articular surfaces is much disrupted then so much greater is the deformity. The anatomical problems involved are of much interest and the chemical and mechanical irritation of vessels and nerves often causes grave circulatory difficulties. The sural nerve behind the ankle joint is much exposed to this and may develop neuromas which, themselves, provide additional foci or irritation. But damage to the vessels is usually more serious than this and the author, first describing the more common course of the arterial supply to the parts, stresses that abnormal arterial formation is common. If one or other of the posterior tibial or peroneal arteries survives then the outlook is fair but if both cease to function grave consequences may ensue. In the early stages of treatment this risk may appear slight but lacerations of smaller branches may cause local thrombosis which, spreading to the main vessel, has disastrous implications. In treating injuries in this region general orthopaedic principles hold good and what is done in the first few hours may have the greatest importance. If the articular surfaces have been sheared off difficulties often occur from the impossibility of controlling the smaller bony fragments and, with much

avascular necrosis of the femoral head. In the third patient, a boy of 12 years, an undisplaced fracture of the neck of the femur led, two years later, to degenerative change in the femoral head. The prognosis, therefore, at the time of injury, should always be guarded. These cases demonstrate the vulnerability of the blood supply to the neck of the femur in children and support the traumatic theory of origin of Perthes' disease.

Intertrochanteric fractures of the femur

A 10-year analysis

CLEVELAND and his colleagues (1959) describe a survey of 239 trochanteric fractures of the femur. The average age of the patients was 75 years and the majority of the injuries occurred in females. The fractures affected the right femur in 44 per cent of cases. Pertrochanteric fractures were recorded in 60·3 per cent of the series, but subtrochanteric fractures were relatively uncommon. Multiple fractures of the hip were sustained in 34 cases. So far as immobilization treatment was concerned, a one-piece Jewett nail, 3–3½ inches in length, was usually employed for internal fixation. In 76 per cent of cases the fixation device was inserted at an angle of 130 degrees. Few cases of wound infection were recorded. Twenty-four patients died before discharge from hospital, but the remaining patients were out of bed after an average period of 15 days and out of hospital after an average period of 53 days. Nine nails broke and one nail became bent. Although there were 23 instances in which the femoral head was penetrated, radiological examination revealed that 80 per cent of the nails were well placed. The end-result was not influenced adversely by the use of the multiple-drive technique. Union of the fracture took place after an average period of 4·5 months had elapsed. When traction was employed instead of nail fixation a longer period was required for union to be completed. The authors point out that, in many cases, use of a little care and foresight would have prevented the accidents. There is a chance of 16·4 per cent that the patient will eventually sustain a second fracture of the hip. With reference to the technique of fixation, if a fully driven nail is used the possibility should be accepted that penetration of the articular cartilage may subsequently take place. Fatigue fracture of the implant is another hazard.

Fracture of the intercondylar eminence of the tibia

MEYERS and MCKEEVER (1959) point out that fracture of the intercondylar eminence of the tibia is most often encountered in children aged 8–13 years. Clinically a large effusion of the knee develops rapidly after trauma. In many cases there is a history of a bicycle accident and a fall on the bent knee, with an internal twist of the tibia on the femur. The joint is held in a flexed position and severe pain is experienced if attempts are made to extend the knee. Muscle spasm causes flexion deformity. In the child there is no lateral instability of the joint and the prognosis for complete recovery is excellent. The fracture is an isolated injury and the supporting ligaments and gliding surfaces of the knee joint are intact. Permanent disability often results in adults, however, for the fracture is likely to be accompanied by severe injury to the supporting structures of the knee. In children radiological examination may show the following types of fracture: Type I, in which there is no displacement of the fragment, Type II, with partial dislodgement of the fragment, and Type III, in which the fragment is completely dislodged. For Types I and II fractures immobilization is required until bone union takes place. Haemarthrosis is aspirated if the joint is under tension. Neither open reduction nor forceful manipulation is needed in the management of these fractures. The lower limb is immobilized in a toe-to-groin cast with the knee joint flexed. Radiological evidence of bone healing is usually obtained after a period of 12 weeks. Type III fracture is treated by open reduction and subseqent immobilization. Metallic internal fixation is not needed, but if retention of the fragment is required an absorbable suture on a cutting needle is passed through the fragment and through the meniscus near the sharp margin. The authors record excellent results in 25 of 27 children with Types I and II fractures and in 5 of 8 children with Type III fractures. Immobilization instead of open reduction was employed in a child with Type III fracture. Non-union resulted, with effusion, a loose body and locking. Arthrotomy was

is plantar flexion of the ankle, slight anterior displacement of the tibia upon the talus; inversion of the ankle and lateral rotation of the tibia on the talus. This torsional impaction is probably the principal agent in producing so-called atraumatic osteochondritis dissecans; failure to recognize it may explain the non-acceptance of osteochondritis dissecans as a fracture. Healing can only take place after reduction and immobilization and then, only by the growth of capillaries from the parent talus across the fracture line. Movement here arrests the process of repair and the fragment becomes imprisoned. Further fragments may break off and be dispersed into the ankle joint, producing synovial irritation and degenerative joint disease. Symptoms in the acute stage are those of inversion sprain: in the first stages of the chronic phase, they are those of osteoarthritis; in Stage IV, fracture-locking may occur. Without surgical intervention duration of chronic symptoms is indefinite. Radiological examination is obligatory and confirms the diagnosis. Conservative treatment yielded disappointing results, a contributory factor being the incidence of atraumatic osteochondritis dissecans which produces few acute symptoms. Types of surgery included arthrotomy, removal of fragment, replacement of the fragment, the last two giving good results. A minimal follow-up period of two years is suggested.

REFERENCES

Berndt, A. L., and Harty, M. (1959). *J. Bone Jt Surg.*, **41A**, 988.
Buhr, A. J., and Cooke, A. M. (1959). *Lancet*, **1**, 531.
Cleveland, M., Bosworth, D. M., Thompson, F. R., Wilson, H. J. Jnr., and Ishizuka, T. (1959). *J. Bone Jt Surg.*, **41A**, 1399.
Coleman, S. S. (1959). *Amer. J. Surg.*, **97**, 43.
Durbin, F. C. (1959). *J. Bone Jt Surg.*, **41B**, 758.
French, P. R. (1959). *Lancet*, **2**, 439.
Jackson, R. W., and Macnab, I. (1959). *Amer. J. Surg.*, **97**, 543.
Meyers, M. H., and McKeever, F. M. (1959). *J. Bone Jt Surg.*, **41A**, 209.
Murley, A. H. G. (1959). *Lancet*, **1**, 24,
Roaf, F. (1959). *Brit. J. clin. Pract.*, **13**, 493.
Sage, F. P. (1959). *J. Bone Jt Surg.*, **41A**, 1489.
Sevitt, S., and Gallagher, N. G. (1959). *Lancet*, **2**, 981.
Smith, J. E. M. (1959). *J. Bone Jt Surg.*, **41B**, 122.
Thompson, K. R., and Friesen, C. M. (1959). *J. Bone Jt Surg.*, **41A**, 1423.
Wallensten, S., Cronestrand, R., and Lugnegård, H. (1959). *Acta chir. scand.*, **116**, 148.
Witt, A. N. (1960). *Reconstruction Surgery and Traumatology*. Vol. 5, p. 15. Basel and New York; Karger.

destruction, early arthrodesis may be the best treatment. The author thinks that it would often be better to treat these injuries forthwith and locally, even with somewhat inadequate resources, in order to obtain early reposition and immobilization. For prolonged transport to more highly developed surgical centres may so jolt and disturb the injured parts that more damage is done then than occurred in the original accident. There should be no hesitation in using adequate sedatives to lessen pain, for satisfactory sleep will do much to preserve the functions of the injured tissues, notably of the nerves. In very grave cases when moist gangrene threatens various types of amputation may be essential.

Comminuted fractures of the calcaneum

Treatment by primary triple arthrodesis

THOMPSON and FRIESEN (1959) report on the use of primary triple arthrodesis in the treatment of 25 patients with comminuted fractures of the calcaneum. The series comprised 24 males and 1 female, aged 20–60 years. Bilateral fractures were present in 4 cases. It was found that severe comminuted fractures were associated with fracture of the surface of the bone at the calcaneo-cuboid joint. Sometimes the talar head showed subluxation at the talo-navicular joint. Five radiological projections were employed in order to evaluate the extent of displacement of the bone fragments. Post-operative serial radiographs revealed that healing had occurred after an average period of 3·2 months. Patients returned to work 3–5 months later. Excellent results were achieved in 21 cases. Minor disorders such as a slight limp were experienced by 3 patients, and an exostosis developed on the neck of the talus in 2 cases. With reference to the technique of the operation, it is believed that the injured talo-calcaneal joint cannot be repaired and that fusion of the joint is required. Moreover, the normal function of the two peritalar joints cannot be restored. The authors recommend an incision of the Ollier type. This incision extends from the region of the extensor tendon near the talo-navicular joint, transects the sinus tarsi and terminates at a point situated one inch inferior to the external malleolus. The sinus tarsi is entered and the calcaneo-cuboid, talo-navicular and talo-calcaneal joints are exposed. After resection of the anterior process of the calcaneus, the calcaneo-cuboid, talo-navicular and subtalar joints are excised. Loose fragments are removed, staples are utilized for internal fixation and a leg plaster-cast is applied. The cast incorporates the plantar wires or pins. From 7 to 10 days after the operation the patient is allowed to walk with the aid of crutches, and during the fourth or fifth week the cast and wires are removed.

Transchondral fractures of the talus

BERNDT and HARTY (1959) discuss transchondral fractures of the talus. The term osteochondritis dissecans was first applied to loose bodies in the ankle joint by Kappis in 1922. In 1932, Rendu reported a case of intra-articular fragmentary fracture of the talus. Since then the terms have been interchangeable, resulting in much misconception of the lesion. In an attempt to clarify the position, 214 cases are reviewed and 11 histories reported. The fracture is a specific type for which the name transchondral fracture is anatomically and aetiologically correct. It is a fracture of the articular surface of a bone produced by a force transmitted from the articular surface of a contiguous bone across the joint and through the articular cartilage to the subchondral trabeculae of the fractured bone. It may occur as a small area of compressed trabeculae, or as an avulsion of an osteocartilaginous flake. The avulsed segment has no soft-tissue attachments, no blood or nerve supply and is therefore susceptible to avascular, aseptic necrosis. Although a traumatic aetiology is generally accepted, much hesitancy exists in accepting osteochondritis dissecans as a fracture. It is not sufficiently realized that fracture may occur without recognizable trauma; that it may be painless; that reduction and immobilization may not produce bone union. Operative findings showed the lesion to be in the middle or anterior half of the lateral border, the damage confined to the lesion and the lateral collateral ligament, and inflicted only by strong inversion of the dorsiflexed ankle. The mechanical importance of the ligament explains the absence of pain in Stage I of the fracture and the symptoms of acute inversion sprain in the following stages. In medial lesions the mechanism suggested

syndromes is likely to be more useful than either in isolation. Another example of the same kind is the clinical and genetical separation of near total deafness of early onset where perhaps a dozen types of what used to be called deaf mutism can now be distinguished. Many other examples have arisen in recent years, as in the clarification of the muscular dystrophies, the separation of sex-linked hydrocephalus due to stenosis or the aqueduct of Sylvius from other forms of aqueduct obstruction hydrocephalus, and the separation of recurrent dislocation of patella in families with joint laxity from other types (Carter and Sweetnam, 1958). Another excellent example is the demonstration that one of the dozen or so genetically distinct syndromes which determine tylosis palmaris et plantaris includes, as part of the gene manifestation, carcinoma of the oesophagus (Howel Evans and his colleagues, 1958; Clarke and his colleagues, 1959). There is need for more such studies, as for instance in the elucidation of the problems of the Klippel-Feil type syndrome and its variants, and in the varieties and inheritance of vascular naevi.

The moral which appears is that from time to time there must be co-operation in research between clinicians and medical geneticists. Even though medically qualified, the geneticist cannot be a specialist in all fields and only a few clinicians have the time to keep sufficiently abreast of the rapid development of genetic knowledge or information to be able to make an adequate analysis.

THE PATTERN OF INHERITANCE OF MORPHOLOGICAL ABNORMALITIES

It is perhaps remarkable that of all single gene traits which are recognized in a human population, about 70 per cent are due to autosomal dominant genes, 25 per cent to autosomal recessive, and the remaining 5 per cent to sex-linked recessive genes. Further, nearly all the simply inherited malformations which can be helped by surgical treatment are inherited as dominant traits (Stevenson, 1959). However, even more anatomical variations are determined by complex genetical mechanisms usually interacting with environmental factors. Both dominant and more complexly determined traits vary in severity from relatively mild conditions such as the minor finger and toe anomalies to very severe malformations, many incompatible with life, and individual traits vary greatly in severity even in affected relatives.

It is by no means as easy as is sometimes supposed to determine whether a particular trait is determined by a dominant gene, by a chance coming together of a specific constellation of genes or by additive multigenic inheritance with a threshold effect. Many of the single genes appear to be irregularly manifest, so missing a generation and causing a failure to reach the expected equality of affected and unaffected offspring of an affected parent. It is difficult to be sure which mechanism applies when failure of manifestation is at all frequent. In a number of conditions, in some families, the trait appears to be inherited in a completely regular dominant fashion while in other families the pattern is equally compatible with a dominant gene which is very irregularly expressed or with another mechanism. It is difficult to know whether these differences are due to a single gene manifestation being sometimes affected by the general genetical condition of the

GENETICS AND SURGERY

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COMBINED CLINICAL AND GENETICAL SEPARATIONS OF SYNDROMES

It is a commonplace to say that cleft palates are not all alike. There are clefts of the soft palate, clefts extending into the hard palate, midline clefts and lateral clefts, with and without hare-lip, and other more sophisticated variations. Some of these differences are of degree, and some are clearly sharp differences without overlap.

Then a whole new spectrum of cleft palates appears if they are looked for in stillbirths and the newborn. In a majority of affected infants there are other deformities. Sometimes they are associated with gross deformities such as anencephaly, or foetal chondrodystrophy or with multiple defects of development of the organs and extremities. There are also a number of situations where cleft palate is paired with one other defect, the best examples being the relatively common cleft palate and talipes, and cleft palate and lumbo-sacral spina bifida. All these types are commonly associated with hydramnios and when identical twins, discordant in respect of cleft palate, occur, there is usually hydramnios in one sac. These children with cleft palate and other defects seldom live even when the combination does not seem incompatible with survival as with cleft palate and talipes. So cleft palate with or without hare-lip is in a very high proportion of cases the sole anomaly in an older patient. Yet an exception is present in the syndrome of cleft palate, syndactyly of the third and fourth digits and symmetrical pits in the lower lip. In this condition viability seems unimpaired.

These findings of clinical or morphological heterogeneity are paralleled by genetical heterogeneity, and if it was feasible to produce a two-way table listing all the clinical variants down one side and the variables of genetical significance across the top—variables such as maternal age effect, sex incidence, type of familial concentration and mode of inheritance (which is possible only in a few cases)—then there would appear in the cells of the table smaller entities more homogeneous in both respects and much more likely to have a common aetiology. The more precise diagnosis, which is what this amounts to, must improve the choice of treatment.

This rather lengthy dissertation on cleft palate must be excused as serving to illustrate a principle, namely, that combined clinical and genetical separation of

stopped in metaphase. It has since been shown that the same results can be achieved simply by allowing the *p*H of the culture medium to rise and then to correct it and continue growth in a rich medium. The next stage was to find a way of displaying the chromosomes without damage. Simple squash techniques were unsatisfactory, but by treating the cells with hypotonic saline solution and then rupturing the nucleus by gentle pressure it proved possible to prepare preparations with chromosomes (which have a length range of from about 1 to 10μ depending on the tissue) spread out without overlapping over an area of perhaps 100–200μ.

Cylologists are now agreed on the identity of all the chromosome pairs and an International numerical classification has been agreed.

Mongolism and "polydyspondilism"

As already mentioned, Lejeune, Gauthier and Turpin (1959) first described the situation in mongolism where one of the smallest chromosomes was found to be represented by three instead of the normal pair. Independently, Jacobs and his colleagues (1959) and Book, Fraccaro and Lindsten (1959) had made the same discovery and published their papers some weeks later. The additional chromosome almost certainly arises in the maturation divisions of the ovum—the high age of mothers of mongols has long been known—and the mechanism termed non-disjunction, whereby both chromosomes of a pair pass into one daughter cell (in this case the ovum as opposed to a polar body) is well known in experimental animals and plants. Subsequently, Turpin and his colleagues (1959) have published an account of a child aged three years with "polydyspondilism" (multiple vertebral abnormalities) who has only 45 chromosomes. Two of the pairs are, however, abnormal and it looks as if there has been exchange of a chromosomal terminal fragment between chromosomes of the pairs (in cytogenetic terms a "translocation" of chromosome material).

Sex chromosome anomalies

Also during the year the chromosome complement of male subjects showing Klinefelter's syndrome and of females with Turner's syndrome have been related to chromosome anomalies. In Klinefelter's syndrome apparent males, who are sterile and usually have small and undescended testes and gynaecomastia, have for some years been known to show sex chromatin bodies characteristic of females in their tissue cells and polymorphonuclear leucocytes. Jacobs and Strong (1959) showed that in one typical case the chromosome complement was 47, this being accounted for by the sex chromosomes being represented by two X chromosomes and one Y chromosome, XXY. These findings have been confirmed repeatedly (in about thirty cases) by other workers.

In some discussions in the literature mention is made of "chromatin positive" Klinefelter and "chromatin negative" Klinefelter syndromes. Klinefelter originally described what we now see on chromosome grounds to be a heterogeneous group of cases. It would seem wrong and misleading, however, to continue to attach his name to both, and it should probably be confined to the chromatin positive cases, that is, those with XXY sex chromosomes. This is another excellent example of a genetical separation which is of value clinically.

families, or to really different aetiologies. In some families the condition is determined by single genes and in others by more complex situations; and in the latter case, differences in the clinical manifestations would be more likely.

It is therefore somewhat hazardous to postulate single gene inheritance in conditions merely because in some families this is suggested by the pattern of inheritance. For example, it is not uncommon to find a father and son or brother with different degrees of hypospadias but almost certainly this is not single gene determined. It is failure to realize how easily simple mendelism can be simulated that leads to over-simplification such as the attribution of diabetes mellitus or malignant hypertension to single dominant genes.

CHROMOSOMAL ABNORMALITIES IN MAN

The year 1959 saw remarkable discoveries of chromosomal abnormalities in man. Only three years previously (Ford and Hammerton, 1956) was the diploid number of 46 chromosomes agreed for man. Early in 1959 came the first firm description of a chromosome abnormality, the presence of three of one small chromosome instead of the usual pair in mongolism (Lejeune, Gauthier and Turpin, 1959). This was speedily confirmed in other publications and since then a whole series of papers have appeared on anomalies of the sex and other chromosomes.

Technical advances

Before reviewing these discoveries it is perhaps of interest to trace the technical advances which have made them possible. For simple morphological studies of human chromosomes it is essential to have a sufficient number of cells at the stage of division, termed metaphase, when the chromosomes become visible as rod-like structures each already split longitudinally but adhering at the centromere preparatory to cell division. The cell nucleus being essentially spherical and the chromosomes in different planes and overlapping each other, it is necessary to find a method of spreading them out on a slide without overlapping for examination and counting.

In the past, tissue culture of sheets of cells resulted in necrosis of cells in the centre, in more and more cells becoming polyploid (with multiples of the usual diploid chromosome number) or otherwise abnormal, and some of those cells with abnormal complement of chromosomes tended to overgrow the others so that normal diploid cells were hard to find. Puck, Cieciura and Robinson (1958) revolutionized this situation by starting cell cultures in the usual way from a small piece of tissue, but, by treating it with trypsin, separated off individual cells from which small new cultures grew. By frequent subculturing after trypsinization it is possible to grow indefinitely cells which are predominantly diploid and of unchanging normal chromosomal appearance.

Experimental geneticists had long known that, by treatment of cells with colchicine, cell division could be arrested at metaphase, and by incubating tissue cultures prepared as above it was possible to procure a sufficient number of cells

stopped in metaphase. It has since been shown that the same results can be achieved simply by allowing the pH of the culture medium to rise and then to correct it and continue growth in a rich medium. The next stage was to find a way of displaying the chromosomes without damage. Simple squash techniques were unsatisfactory, but by treating the cells with hypotonic saline solution and then rupturing the nucleus by gentle pressure it proved possible to prepare preparations with chromosomes (which have a length range of from about 1 to 10μ depending on the tissue) spread out without overlapping over an area of perhaps 100–200μ.

Cytologists are now agreed on the identity of all the chromosome pairs and an International numerical classification has been agreed.

Mongolism and "polydyspondilism"

As already mentioned, Lejeune, Gauthier and Turpin (1959) first described the situation in mongolism where one of the smallest chromosomes was found to be represented by three instead of the normal pair. Independently, Jacobs and his colleagues (1959) and Book, Fraccaro and Lindsten (1959) had made the same discovery and published their papers some weeks later. The additional chromosome almost certainly arises in the maturation divisions of the ovum—the high age of mothers of mongols has long been known—and the mechanism termed non-disjunction, whereby both chromosomes of a pair pass into one daughter cell (in this case the ovum as opposed to a polar body) is well known in experimental animals and plants. Subsequently, Turpin and his colleagues (1959) have published an account of a child aged three years with "polydyspondilism" (multiple vertebral abnormalities) who has only 45 chromosomes. Two of the pairs are, however, abnormal and it looks as if there has been exchange of a chromosomal terminal fragment between chromosomes of the pairs (in cytogenetic terms a "translocation" of chromosome material).

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Ford and his colleagues (1959c) have published a remarkable case of Klinefelter's syndrome in a male mongol where the chromosome number is 48, the two extra chromosomes being the additional X to the XY pair characteristic of Klinefelter's syndrome (XXY) and the additional small chromosome characteristic of mongolism. Finally, Baikie and his colleagues (1959) have published a case of a female with 47 chromosomes who has an XXX complement of sex chromosomes. This is characteristic of the "super female" of drosophila.

These findings are of great importance in establishing the occurrence in man of phenomena well known in experimental animals, and in demonstrating differences in the sex determination importance of the sex chromosomes between insects and man. In drosophila the XXY individual is morphologically female but is sterile. In man the XXY karyotype determines Klinefelter's syndrome with male genitalia and characteristics, although with sterility and some slight feminization.

In drosophila the XO fly is morphologically a male, but is sterile. In man the XO individual is in appearance female and usually has developmental anomalies, as described, and primary amenorrhoea.

In drosophila XXX is a weakly female who seldom survives beyond a few days. Only the one case noted above is so far known in human beings, but at least she grew up and it is not inconceivable that such females could be fertile. (She would be expected to have some XXX daughters and XXY (Klinefelter) sons.) Up to this point it seemed possible that the Y chromosome always determined a morphological male. However, Nilsson and his colleagues (1959) published an account of a case of an apparently normal girl with haemophilia who had an XY chromosome pair. Subsequently, Harnden and Stewart (1959) described a "tall eunuchoid female" who has the normal chromosome number of 46 with an XY sex pair. So at least the Y chromosome does not inevitably determine male gonads. Finally, Harnden and Armstrong (1959) recorded a case of a true hermaphrodite, in the sense that one gonad was predominantly testis and the other wholly ovary, who had an XX sex chromosome complement.

It is difficult to know how frequently these chromosomal aberrations occur in man, but clearly any sex development disorders should be thoroughly investigated cytologically. They would perhaps be met with most frequently by gynaecologists, paediatricians, and genito-urinary surgeons.

Conclusion

It seems possible that non-disjunction in autosomes other than the one conveying mongolism may in sum have a frequency as high as mongolism (about 2 per 1,000 births). The speed with which we add to our present knowledge seems likely to depend, in large part, on the frequency with which paediatricians and surgeons refer likely subjects. Thorough investigation of families may be required in some cases for mild effect aberrations, particularly in translocations. Such changes could determine curiously segregating syndromes where more than one type of anomaly, or anomaly plus embryonic wastage occurred in the same family. In our present state of knowledge it would seem that the other types of cases in which chromosomal abnormalities will most likely be found are, in decreasing order of likelihood: (1) unique non-recurring or extremely rare malformations such as

Ford and his colleagues (1959a) demonstrated that in a female with Turner's syndrome of ovarian dysgenesis who lacked sex chromatin bodies in cell nuclei, the chromosome complement was 45; the missing chromosome was from the sex chromosomes where there was an X but no partnering X or Y, so that the karyotype in respect of the sex chromosomes was XO. This has again been confirmed repeatedly by other workers.

In Turner's syndrome the females are small, usually showing signs of infantilism at an early age and there are often associated abnormalities such as webbed neck, cubitus valgus and coarctation of the aorta (which is otherwise almost confined to males). The children are usually severely retarded in mental as well as physical growth. Older cases may present complaining of primary amenorrhoea and failure of breast development. The ovaries are characteristically absent or small and atrophic. The relationship of Turner's syndrome in males with a normal XY complement is not clear and it seems likely that the term should be confined to the types of females (as above) first described by Turner who were probably of XO karyotype. Some work as yet unpublished is likely to demonstrate that some of the features of Turner's syndrome can be determined by non-disjunction at a larger autosome than the one involved in mongolism.

It would appear that these sex chromosome anomalies, as in mongolism, are determined by non-disjunction. It is not absolutely clear whether this occurs more frequently or consistently in the male or female parent. Studies are continuing in families where sex linked red-green colour blindness is a segregating factor. Analysis of the findings should throw light on the more probable parent in whom nondisjunction occurred at germ-cell maturation in given cases and on the question as to whether the non-disjunction occurs at the first or second meiotic divisions.

Ford and his colleagues (1959b) have described a man with Klinefelter's syndrome, two-thirds of whose cells showed the sex chromosomes XXY and one-third the karyotype XX. This is interpreted as due to mosaicism presumably determined either by fertilization of an XX ovum arising by non-disjunction by a Y bearing sperm, or by fertilization of a normal X ovum by a non-disjunction XY sperm. Following this perhaps the Y was lost in some cell by non-disjunction at an early stage of embryonic development. Alternatively, at an early stage in a male in embryonic development, perhaps in the morula or blastocyst stage, an XX non-disjunction occurred.

Some idea of the frequency of Klinefelter's syndrome may be deduced from the findings of Moore (1959) who examined cells from oral smears of 1,911 male and 1,804 female newborn babies. Nuclear and anatomical sex corresponded in all females, but five anatomical males (0·4 per 1,000) had sex chromatin in their cells. It seems essential that this work be repeated and the chromosomes examined in cases where nuclear and anatomical sex are discordant.

It is of interest to note that Bassoe (1956) has published an instance of Klinefelter's syndrome and Turner's syndrome in sibs. This could readily be explained in terms of a repeated non-disjunction at meiosis resulting in some gametes which lacked X or Y and some which had XY or XX.

If neither parent shows the trait, but one child has been affected, then it may be presumed, in a completely manifest gene trait, that a fresh mutation has arisen. It is very unlikely that a second independent mutation would arise in either parent but there is a very small additional risk to subsequent children. Delayed mutation which is not manifest in the first recipient, or mutation far back in the germ tract determining a germinal mosaic may mean that a proportion of all mature ova or (more likely) sperms carry a mutation received from its ancestor. The overall risk, however, is small and could arbitrarily be given as about one in twenty.

If neither parent shows the trait but two or more children suffering from a dominant gene trait have been born to them, it must be presumed that one of the above mechanisms is operative. In that case the risk is less than half to subsequent children, but is still very high, and could be assessed as between half and one-eighth.

When one parent is affected

In this case, irrespective of whether there are any children affected or not, when the gene is dominant and regularly expressed, the risk to each child must be assessed as half.

Traits determined by incompletely penetrant dominant genes

If the condition is determined by an incompletely penetrant dominant gene, as demonstrated by occasional missing of a generation in the pedigree, or a failure of the offspring of affected parents in a large pedigree to be affected and unaffected in equal proportions or both circumstances apply, then the situation is more complex.

If one parent is affected then the risk to each child is rather less than half but the difference is so small as to be ignored. When, however, one of the parents is not affected but is in direct line of descent from an affected person, the situation is more complex and no simple method of estimating risks can be given. It is probably wise to seek expert advice in such situations.

Traits determined in a more complex manner

Advice is more commonly sought, however, in respect of anomalies where the genetic factors are ill understood, if only because the total frequency of such conditions is greater than of those determined by clear-cut dominant genes. This group includes almost all the "congenital abnormalities" as listed in the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* which is used by the Registrar General for national mortality statistics.

In these conditions all we know is that if it has occurred in one child, it tends to occur with greater frequency in subsequent sibs than in the general population. In many of these conditions the intra-uterine environment is probably of as great importance as the genotype of the child. In some, notably mongolism, there is a rapidly increasing risk with rising maternal age. Some are more common in first and some in later pregnancies, and there is a strong association with hydramnios complicating the pregnancy. Very empirically, the risk to a child not preceded by one so affected is the same as the risk in all births which is always so low as to be disregarded. It should be remembered, however, that perhaps 2 per cent of all live

gross developmental abnormalities of skeleton or major organs or both; (2) early abortion material, particularly where associated with gross failure of the embryo to develop properly; (3) uncommon abnormalities of development, even if the type is repeated, where there are disturbances of bodily proportions, peculiar limb shapes, short necks and abnormal palm print patterns; (4) conditions present at birth which are currently attributed to inheritance of a single dominant gene.

The specimen required is easily obtained by lifting a hair with forceps and then snipping off the skin pulled up at the base. This procedure is no more painful than venepuncture if the conjunctival scissors used are sharp. Material which will grow can also be obtained at necropsy of the recently dead, from internal organs. The material, however, should always be placed at once in one of the special media. From newborn infants a piece of umbilical cord, as sterile as possible, is a suitable specimen.

PRINCIPLES OF ESTIMATING GENETICAL RISKS

It is reasonable to ignore autosomal and sex-linked recessive traits in the context of surgical practice. The risks can then be considered under the heading of conditions determind by single dominant genes and those where the mode of inheritance is more complex.

Estimation of risks can be, at one end of the scale, extremely simple as when determined by a completely manifest single dominant gene mechanism. At the other extreme, a reasonable estimate can only be made after a thorough investigation of the family and with a wide knowledge of the population frequency and familial incidence of the trait. Medical geneticists usually find that the estimate of risk which they make is considerably smaller than that made by their clinical colleagues.

If there is any doubt about a risk, advice should be sought from a medical geneticist but he must be given a reasonable time to formulate an opinion. Even in apparently clear-cut situations the geneticist will need to investigate the family and usually he will want to discuss the diagnosis with the clinician. This latter may seem presumptuous but it is not a question of doubting the diagnosis, rather that the diagnostic label not infrequently describes a heterogeneous group of conditions, and the kind of separation of importance to the geneticist is not necessarily of importance to the clinician.

Trait determined by a single dominant gene—fully penetrant

A common situation where advice is sought is that of parents or prospective parents asking about the risk of a child being affected in some specific way. If the condition is determined by a completely manifest dominant gene then the risks are as follows.

Where neither parent is affected

If neither parent shows the trait and there are as yet no children or no affected children, then as the condition is always manifest if the gene is carried, neither parent has the gene and the condition cannot be handed on to the child. (The risk of a fresh mutation arising in either parent is extremely small.)

Jacobs, P. A., and Strong, J. A. (1959). "A Case of Human Intersexuality Having a Possible XXY Sex-determining Mechanism." *Nature, Lond.*, 183, 302.
— Baikie, A. G., Court Brown, W., and Strong, J. A. (1959). "The Somatic Chromosomes in Mongolism." *Lancet*, 1, 710.
Lejeune, J., Gauthier, Marthe, and Turpin, R. (1959). "Les chromosomes humaines en culture des tissus." *C.R. Acad. Sci., Paris*, 248, 602.
Moore, K. L. (1959). "Sex Reversal in Newborn Babies." *Lancet*, 1, 217.
Nilsson, I. M., Bergman, S., Reitalu, J., and Waldenstrom, J. (1959). "Haemophilia A in a 'Girl' with Male Sex Chromatin Pattern." *Lancet*, 2, 264.
Puck, T. T., Cieciura, S. J., and Robinson, A (1958). "Genetics of Somatic Mammalian Cells, III. Long term Cultivation of Euploid Cells from Human and Animal Subjects," *J. Exp. Med.* 108, 945.
Stevenson, A. C. (1959). "The Load of Hereditary Defects in Human Populations." *Rad. Res., Suppl.* 1, 306.
Turpin, R., Lejeune, J., Lafourcade, J., and Gauthier, Marthe. (1959). "Aberrations chromosomiques et maladies humaine. Sa , olydyspondylie a 45 chromosomes." *C. R. Acad. Sci., Paris*, 248, 3636.

SELECTED ABSTRACTS

Chromosome aberration in human disease

A case of "polydyspondilism"

TURPIN and his colleagues (1959) discussed chromosome abnormalities and human disease. In the case discussed, the malformation "polydyspondilism" involved three regions of the spine: the cervical, thoracic and sacral. Elsewhere, there was moderate enlargement of the vertebral canal in the cervico-thoracic region, and closure of the sella turcica. Somatic development was retarded; slight mental retardation was present. Examination by culture of fibroblasts and chromosome analysis revealed 45 instead of 46 chromosomes. In three different biopsies 33 cells and particularly 14 karyotypes, revealed the absence of a small acrocentric chromosome. The apparent absence of one of the small acrocentric chromosomes is, however, compensated for by the constant presence of a small deeply staining segment attached to one of the usually small heterochromatic arms of one of the larger chromosomes. This may be the missing acrocentric chromosome and it is postulated that the chromosomal rearrangements have determined the clinical syndrome.

Human chromosomes in tissue culture

LEJEUNE, GAUTHIER and TURPIN (1959) presented a paper on human chromosomes studied in short-term culture of fibroblasts. The presence of four small semi-acrocentric chromosomes in woman and five in man enables a diagnosis of chromosome sex to be made. (Two pairs of small acrocentric autosomes being somewhat difficult to differentiate from the Y chromosome.) In three boys with mongolism this criterion did not hold. There were in all 47 chromosomes (there being an additional acrocentric autosome). A fragment of fascia lata is cultured and a single cell bed or layer is obtained. Rupture of the cell nuclei by treatment with hypotonic saline solution frees and displays the chromosomes. The preparations are photographed on 35 millimetre microphile film and enlarged negatives prepared. Some seven subcultures over about a month are necessary to get good preparations. The diploid chromosome number is very constant but in older cultures a greater variation is found. The exact identification of the two X chromosomes in the female is not easy because they so closely resemble three of the larger autosome pairs. (Later papers by these authors show a greater confidence in chromosome identification which is shared by other authors.)

A sex-chromosome anomaly in Turner's syndrome

Case report

FORD and his colleagues (1959) reported on a chromatin-negative case of Turner's syndrome, or gonadal dysgenesis, in which the bone-marrow cells contained 45 instead of 46

and stillborn children suffer from some abnormality which may range from being lethal, like anencephaly, to trivial, or to those which are recognized only relatively later in some cases, such as congenital heart disease. Some caution is advisable, therefore, in discussion with parents and such phrases as "no risk whatever" can lead to recrimination at a later date.

If, however, one child has been affected with an anomaly such as anencephaly, oesophageal stenosis or fistula, or certain types of congenital heart disease, then the risk to subsequent individual children is increased probably to about ten times that in the population, but even so the risk is still relatively small. If, however, two cases have occurred in a sibship the risk to subsequent children is very much increased.

In a number of conditions where in some cases simple and in others more complex mechanisms can result in the same defect, all the family evidence available must be used and care must be taken, when the family history is not helpful, to allow for the high risks if the condition be determined by single genes. In such cases the relative frequency of single gene cases to the total, the sex of the presenting case, the association with hydramnios, maternal age and differences in the clinical condition, must all be taken into account even if it is impossible to assign a proper weighting to each. Again, therefore, consultation is advisable in that, although any estimates made must be rough, it is important not to miss indications whose importance would more likely be noted by a geneticist.

REFERENCES

Baikie, A. G., Court Brown, W., McGregor, T. N., Maclean, N., and Harnden, D. G. (1959). "Evidence for the Existence of the Human 'Super Female'." *Lancet*, **2**, 423.

Bassoe, H. H. (1956). "Familial Congenital Muscular Dystrophy with Gonadal Dysgenesis." *J. clin. Endocrin.* **16**, 1614.

Book, J. A., Fraccaro, M., and Lindsten, J. (1959). "Cytogenetical Observations on Mongolism." *Acta paediat., Uppsala*, **48**, 453.

Carter, C. O., and Sweetnam, R. (1958). "Familial Joint Laxity and Recurrent Dislocation of the Patella." *J. Bone Jt Surg.*, **40B**, 664.

Clarke, C. A., Howel Evans, W., McConnell, R. B., and Sheppard, P. M. (1959). "Carcinoma of Oesophagus in Association with Tylosis." *Brit. med. J.*, **2**, 1100.

Ford, C. E., and Hammerton, J. L. (1956). "The Chromosomes of Man." *Nature, Lond.*, **178**, 1020.

— Jones, K. W., Polani, P. E., de Almeida, J. C. C., and Briggs, J. H. (1959a). "A Sex-chromosome Anomaly in a Case of Gonadal Dysgenesis (Turner's Syndrome)." *Lancet*, **1**, 711.

— Polani, P. E., Briggs, J. H., and Bishop, P. M. F. (1959b). "A Presumptive Human XXY/XX Mosaic." *Nature, Lond.*, **183**, 1030.

— Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., and Shapiro, A. (1959). "The Chromosomes in a Patient Showing Both Mongolism and the Klinefelter Syndrome." *Lancet*, **1**, 709.

Harnden, D. G., and Armstrong, C. N. (1959). "The Chromosomes of a True Hermaphrodite." *Brit. med. J.*, **2**, 1287.

— and Stewart, J. S. S. (1959). "The Chromosomes in a Case of Pure Gonadal Dysgenesis." *Ibid.*, **2**, 1285.

Howel Evans, W., McConnell, R. B., Clarke, C. A., and Sheppard, P. M. (1958). "Carcinoma of the Oesophagus with Keratosis Palmaris et Plantaris." *Quart. J. Med.*, **27**, 413.

from an XXY zygote. Development may have been initiated by fertilization of a non-disjunctional XX egg by a Y sperm. Alternatively, a normal X egg may have been fertilized by a non-disjunctional XY sperm.

Familial joint laxity and recurrent dislocation of the patella

Case history

CARTER and SWEETNAM *(1958) described a case of familial joint laxity associated with* recurrent dislocation of the patella. The condition was observed in a boy, aged six years, with a history of recurrent dislocation of the right patella about once every month during the course of two years. Examination revealed abnormal lateral mobility of the right patella with 30 degrees of abduction and 10 degrees of adduction on straining. The left knee also showed instability. Abnormal laxity was evident in the shoulders, elbows, wrists and metacarpo-phalangeal and interphalangeal joints. At operation the only significant abnormality was pronounced atrophy of the medial capsule and patellar retinaculum. The patella was fixed into place by means of a loop of the quadriceps expansion and part of the patellar ligament. In addition, the semitendinosus was transplanted to the medial border of the bone. When the boy's family pedigree was investigated it was ascertained that three members had a history of recurrent dislocation of the patella and abnormally lax knees with hypermobility of other joints. A fourth member had probably suffered from a single dislocation. Joint laxity without dislocation was recorded in five relatives. The pattern of inheritance was that of a dominant gene which had probably arisen as a mutation in the boy's great-grandfather.

REFERENCES

Carter, C., and Sweetnam, R. (1958). *J. Bone Jt Surg.*, **40B**, 664.
Ford, C. E., Polani, P. E., Briggs, J. H., and Bishop, P. M. F. (1959). *Nature, Lond.*, **183**, 1030.
— Jones, K. W., Polani, P. E., de Almeida, J. C., and Briggs, J. H. (1959). *Lancet*, **1**, 711.
— — Miller, O. J., Mittwoch, Ursula, Penrose, L. S., Ridler, M., and Shapiro, A. (1959). *Ibid.*, **1**, 709.
Lejeune, J., Gauthier, Marthe, and Turpin, R. (1959). *C. R. Acad. Sci., Paris*, **248**, 602.
Turpin, R., Lejeune, J., Lafourcade, J., and Gauthier, Marthe (1959). *Ibid.*, **248**, 3636.

chromosomes. The sex-chromosomal constitution was determined as XO. The patient, a female aged 14 years, was of short stature and educationally retarded. Examination of the face revealed slight asymmetry, a small chin and low implantation of the ears. The palate was high arched and the neck was short. Abnormalities included digital deformities, slight funnel deformity of the chest, cubitus valgus and pes cavus. Secondary sex characteristics were absent and there was primary amenorrhoea. Skin biopsy and blood smears revealed a chromatin-negative pattern. On cytological processing of the bone marrow by means of the colchicine technique and the Feulgen staining procedure, 99 of 102 cells were found to contain only 45 chromosomes. Four small acrocentric chromosomes were present, as in the normal female, and there were 15 metacentric chromosomes of medium length, as in the normal male. Although the cells were "male" as judged by nuclear sexing the chromosomes contained no male component. The authors are of the opinion that the terms, chromatin negatively or positively, should be employed instead of the term nuclear sexing. If the chromosomal constitution is XO the case should not be regarded as an instance of sex-reversal. Such a patient is neither a chromosomal nor a genetic male. The sex is female, but the genotype is abnormal.

Chromosomes in a patient with mongolism and Klinefelter's syndrome

Ford and his colleagues (1959) gave an account of a male imbecile, aged 45 years, with signs of mongolism and Klinefelter's syndrome. The father was aged 40 years and the mother was 42 when the patient was born. His parents were not consanguineous. In addition to pronounced mongoloid traits the patient had scanty facial, axillary and pubic hair, small testes, slight gynaecomastia and feminine distribution of fat. Despite these abnormalities the general health was satisfactory. Testicular biopsy showed an advanced stage of atrophy. Cells of the skin and buccal mucous membrane contained the Barr chromatin body and the leucocytes showed drumstick appendages. Examination of bone-marrow specimens revealed cells with 48 chromosomes comprising 23 pairs, a Y chromosome and an acrocentric chromosome. The authors point out that the findings represent the first recorded case of a human being with two supernumerary chromosomes. The additional sex chromosome is a typical finding in Klinefelter's syndrome and the additional small chromosome may be characteristic of mongolism. In this context, Jacobs and Strong have found 47 chromosomes in the cells of a patient with Klinefelter's syndrome and Lejeune, Gautier and Turpin have reported on three cases of mongolism in which a small extra chromosome was detected in tissue cultures derived from the connective tissue.

A presumptive human XXY/XX mosaic

Ford and his colleagues (1959) reported on a specimen of marrow obtained by sternal puncture in a chromatin-positive case of Klinefelter's syndrome. After cytological processing 65 cells were regarded as suitable for counting. The number of chromosomes ranged from 41 to 49, but in 44 cells the count was found to be 47. It was not possible to identify the individual X and Y chromosomes. Twelve cells with 47 chromosomes were selected for analysis. All contained 5 very short acrocentric chromosomes with 16 short chromosomes, as in the male, and 16 chromosomes of medium length, as in the female. The remaining chromosomes were distributed in 5 long pairs, a distribution which is common to both sexes. Apparently the cells contained 2 X-chromosomes and a single Y-chromosome, as well as 22 pairs of autosomes. In 5 of 11 cells with counts of 46, examination revealed an apparently normal female set, with 4 small acrocentrics and 16 other short chromosomes. There were 16 chromosomes of medium size and the remaining chromosomes were long. Many more cells with a count of 46 were found than would be expected from damage alone. Presumably mitotic non-disjunction and loss of the Y-chromosome had played a part in the evolution of these cells. Loss of the Y-chromosome from an XXY cell would represent a movement towards normality. On the other hand, loss of an autosome would give rise to a deficient cell. Hence it is assumed that the 46-chromosome cell contains the normal female complement of 2 X-chromosomes and no Y-chromosome. The case of Klinefelter's syndrome is a true XXY/XX mosaic derived

THE APPARATUS

The apparatus consists of an artificial heart and a heat exchanger (Fig. 46).

The heart

The heart comprises two De Bakey type pumps simulating the ventricles and two plastic reservoirs with translucent walls placed side by side about 20 inches below heart level. The reservoirs are 10 inches long and 2½ inches in diameter and receive blood from the atria. They can thus be regarded as extensions of these chambers. They are each primed with 400-500 millilitres of fresh heparinized blood.

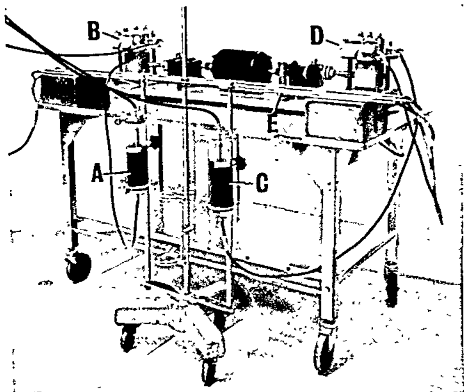


Fig. 46.—The apparatus. (A) Right atrial reservoir (systemic venous blood enters at top). (B) Roller pump transmitting blood from this reservoir to pulmonary artery. (C) Left atrial reservoir (pulmonary venous blood enters at top). (D) Roller pump transmitting blood from this reservoir to aorta via (E) stainless steel tubes arranged in parallel. (These are normally suspended in a trough through which hot or cold liquids are passed to effect heat exchange.)

The heat exchanger

The heat exchanger is placed between the left ventricular pump and the systemic arterial inflow. It consists of stainless steel tubes, polished inside, which are of ¼-inch internal diameter and 60 inches in length. These are arranged in parallel

PROFOUND HYPOTHERMIA IN CARDIAC SURGERY

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The most spectacular advance in cardiac surgery during the last five years has been the development and widespread use of the pump oxygenator for cardio-pulmonary by-pass and operations in the opened heart.

Many machines of various designs have been proved successful by clinical use but maintenance is time consuming, their large priming volume makes great demands on blood banks, and even the best artificial oxygenator is still inferior to the human lung.

The use of hypothermia in cardiac surgery stems from experimental studies on surface cooling carried out in Toronto by Bigelow and his colleagues (1950). The first successful clinical application was reported by Lewis and Taufic (1953) in the closure of an atrial septal defect. However, its early promise as a simple solution to the difficulties of visual intracardiac surgery was not completely fulfilled. Experience has shown that it is dangerous to cool a patient below an oesophageal temperature of 30°C. because ventricular fibrillation frequently occurs and may be irreversible until the patient is rewarmed. This is impossible without an effective circulation. The use of anti-fibrillation drugs has not yet improved the position.

At 30°C. complete circulatory arrest is safe for 8–10 minutes, sufficient time only for the correction of simple intracardiac abnormalities, such as pulmonary valve stenosis and persistent ostium secundum. This allows no margin for error in pre-operative diagnosis or for unexpected difficulties once the heart is opened. The limitation of hypothermia, whether induced by surface or venovenous methods, is due to the failure of the diseased human heart itself as it is cooled. Respiratory muscle failure which also occurs during hypothermia is readily corrected by the use of an endotracheal tube and controlled respiration. In similar fashion circulatory failure might be overcome by using mechanical pumps instead of the heart. A heat exchanger in the extracorporeal circuit could be used to cool and rewarm the body through a wide temperature range. This is the essence of the experimental studies and their subsequent clinical application reported by Drew and Anderson (1959) and Drew, Keen and Benazon (1959).

The importance of the technique largely rests in the apparatus and its method of use which is new enough to warrant description.

The approach to the heart is usually through a median sternotomy. The patient is then given heparin 1·5 milligrams per kilogram body weight. A cannula is placed in the left atrium, usually through the appendage, and held in position by a purse string suture, the ends of which are threaded through a soft rubber tube and used as a snare. All cannulations in the chest are made secure in this way. Blood is then allowed to drain into the left atrial reservoir. The amount is controlled by an adjustable stop on the venous line and varies between 150 millilitres per minute in an infant to about 1,000 millilitres per minute in an adult. The same volume is pumped from the reservoir, through the heat exchanger into the femoral artery. Cooling is rapid and eventually the circulation will begin to fail, either because of poor ventricular contraction or the onset of ventricular fibrillation. A cannula previously placed in the right atrium is then allowed to drain blood into the right venous reservoir. From here blood is pumped into the pulmonary artery through a cannula inserted in the infundibulum of the right ventricle (Fig. 48). (In cases of atrial septal defect it is sometimes convenient to insert both atrial cannulae through the right atrial wall, placing the left cannula in its correct position during the period of circulatory arrest.)

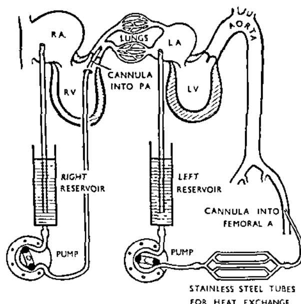


FIG. 47.—Method of use of artificial heart and heat exchanger. (*By courtesy of the Editor of Anaesthesia.*)

The flow through the pumps is then increased and the stops on the venous lines gradually removed. The systemic flow is regulated to give a mean blood pressure of at least 70–80 mm. Hg. This determines the amount of blood returning to the right atrial reservoir and the right ventricular pump is adjusted to keep the reservoir levels constant. Stabilization is rapidly achieved and little readjustment is required. Sometimes the pumps will be working at different speeds to maintain a constant reservoir level. A higher left pump output is frequently found in cases of Fallot's tetralogy presumably due to a shunt of blood from the aorta to the

using Y-shaped connecting pieces and short lengths of plastic tube. Two, four or eight steel tubes are used depending upon the size of the patient. They are suspended in a trough through which is passed cold or warm liquids to effect heat exchange. The temperature of the water bath is kept at 2°C. during cooling and at 42°C. during rewarming. This heat exchanger has the merit of simplicity. Its parts are inexpensive, it can be easily cleaned and its size can be varied according to the weight of the patient. The use of several connecting pieces is clumsy but allows equal distribution of blood through the tubes. This is an important factor governing the efficiency and safety of any heat exchanger and is easily overlooked.

The cannulae

There are four cannulae, one for each atrium and the others for the pulmonary and femoral arteries. They are made in various sizes and fashioned from thin-walled stainless steel tubes to give the biggest possible lumen. A straight cannula with a fenestrated end appears to be the most convenient type for insertion through the atrial appendage. Short straight cannulae are used in the femoral artery and for insertion high in the infundibulum of the right ventricle into the pulmonary artery. A rigid pulmonary artery cannula is essential when there is right ventricular outflow tract obstruction. The arterial lines require to be anchored a short distance from the cannulae to prevent them being dislodged particularly when high flows are being used.

In 65 perfusions there have been two accidents associated with cannulation. Both involved the pulmonary artery, although this is perhaps the easiest cannulation to perform. In one case a very long steel cannula was used which became impacted in the artery to the right upper lobe. This was perfused by a flow greater than its capacity and resulted in severe lobar pulmonary oedema and a fatal outcome. In the second case a similar cannula was left *in situ* during manipulation of the heart and the artery was damaged. Since these mishaps which occurred early in the series, a short cannula has been used, the tip of which reaches only into the main trunk. Great care is used when the heart is handled if the cannulae are still in position.

The parts of the apparatus are joined together by translucent tubes made of polyvinyl chloride. This is of ¼-inch internal diameter when flows up to 2 litres per minute are anticipated and ⅜-inch internal diameter for flows exceeding this amount.

The apparatus is primed with fresh heparinized blood which has varied between 1,000–2,500 millilitres depending upon the size of the patient.

METHOD OF USE

The following is the method of use (Fig. 47) of the artificial heart and heat exchanger.

Inguinal incisions are made to mobilize the femoral arteries. The left artery will be cannulated and the right artery will receive a catheter to record continuously the central aortic pressure. This is done after the patient is heparinized and the heart has been exposed.

resistance. The discrepancies between the pump flows have never been marked enough to cause serious concern.

With the establishment of artificial pulmonary and systemic circulation, cooling proceeds until a level of 13°–15°C. is recorded in the nasopharynx. This may take less than 30 minutes in an infant or small child and perhaps twice this time in a heavy adult.

It was found experimentally that the nasopharyngeal temperature fairly accurately reflects brain temperature. This does not represent body temperature because it is common to find the oesophageal temperature several degrees lower while the muscle temperature may be well above 15°C. (Fig. 49). No single temperature recording is completely reliable. An intracavitary temperature may be influenced for example by a pool of secretion or in the rectum by the presence of faeces. An intramuscular electrode may be insulated by a haematoma which may develop in the heparinized patient. In practice the temperatures are continuously monitored at various points using a multichannel recorder. This enables cooling to be controlled so that the temperature gradients between various parts

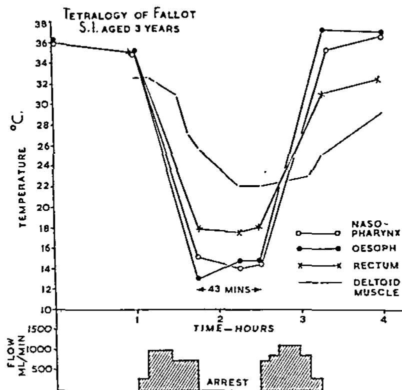


FIG. 49.—Graph showing variation in cooling and rewarming at different sites. When the temperature in the nasopharynx is 15°C. it is 13°C. in the oesophagus and 26°C. in the deltoid muscle.

left atrium via the increased bronchial circulation. A patent ductus arteriosus would probably produce the same effect but so far we have not been in a position to confirm this happening. In cases of severe left-to-right shunt through the cardiac septum with a grossly dilated pulmonary artery, there may be some regurgitation through the pulmonary and tricuspid valves which will lead to a higher speed through the right ventricular pump.

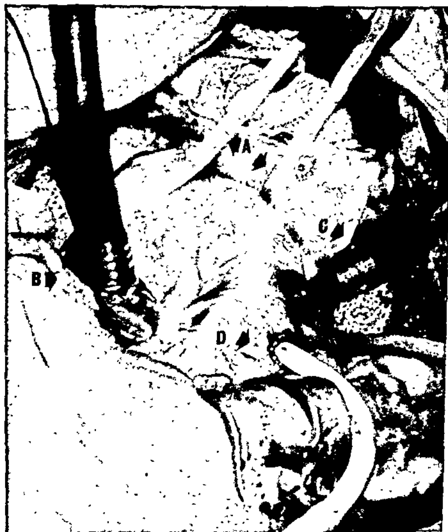


FIG. 48.—The arrangement of the cannulae. (A) Tape around aorto-pulmonary trunk. (B) Cannula in right atrium. (C) Cannula in left atrium. (D) Plastic cannula in pulmonary artery inserted via a stab incision high in the right ventricle. (A short stainless steel cannula is now recommended and is essential in cases of outflow obstruction.)

Before each operation the pumps are set to be just occlusive. If the adjustment is not accurate it may result in unequal pump speeds, particularly if the left pump is non-occlusive, because this is working against the higher systemic

THE IMMEDIATE RESULTS

Profound hypothermia has been used in over 60 cases for the treatment of congenital and acquired heart disease, including most types of septal defect, endocardial cushion abnormalities, Fallot's tetralogy and acquired aortic and mitral valve lesions.

The ages of the patient varied between 3 months and 55 years and the weight ranged from 8 pounds (4 kilograms) to 188 pounds (83 kilograms).

The number of patients in each category is not large enough to warrant firm conclusions, but the immediate mortality and morbidity bears favourable comparison with other methods used for open heart surgery.

The apparatus is reliable. Haemolysis is low and there is no serious electrolyte disturbance except in patients with chronic cardiac failure in whom electrolyte imbalance already exists. The only notable feature in the studies which have been done is a tendency for the plasma potassium to be on the low side of normal after rewarming.

No patient has had less than 25 minutes and a few patients have had more than 50 minutes circulatory standstill without harm. There has been no evidence of cerebral damage which with certainty can be attributed to the long periods of circulatory and respiratory arrest. Two patients, aged about 50 years, with calcific aortic stenosis, showed very slight mental aberration for the first few days post-operatively but then became completely normal. The changes in both may have been associated with circulatory arrest, but may have been due to cerebral air embolism after aortotomy or calcific embolism following surgery on a grossly calcified valve. It is not uncommon to observe similar temporary character change after mitral valvotomy using a closed technique at normal temperatures.

One patient died of surgical bleeding from the left atrium. Another was reopened three hours after operation because of a leaking aortic suture line. The blood pressure was lowered using Arfonad, the leak repaired and the patient recovered. One patient bled profusely from the start of the operation and lost 1,500 millilitres of blood before cannulation of the heart. Although there was no obvious cause for this, the haemorrhage continued after the operation and he died. Since this episode all patients now undergo a more thorough pre-operative assessment for bleeding tendencies and clotting deficiencies. This has resulted in some patients being temporarily rejected for surgery. However, no marked bleeding tendency has been observed in the series as a whole and most patients require only small additional post-operative transfusion.

COMPARISON BETWEEN PROFOUND HYPOTHERMIA AND CARDIO-PULMONARY BY-PASS

The apparatus described is more simple than the heart-lung machine used for cardio-pulmonary by-pass. An artificial oxygenator and a coronary sinus suction system is not required. A filter is not used except in cases of mitral valve disease. Stainless steel gauze discs are then placed at the bottom of the reservoirs to trap particulate material that may come from the atria.

Less blood is needed to prime the extracorporeal circuit. The cannulation

of the body are not unduly high. It also provides a check on the nasopharyngeal reading.

At 13°–15°C. the pumps are stopped and artificial respiration ceases. Clamps are placed on the venae cavae. The heart is now drained of blood through the venous lines. An aortic clamp is applied to prevent air embolism once the heart is opened.

The appropriate surgery on the heart and neighbouring great vessels may now be undertaken removing temporarily any cannulae which obstruct the approach. When this is completed air is displaced in the following way.

After right atriotomy or ventriculotomy, near the completion of septal and wall repair, a few turns are made manually on the left ventricular pump after removing the caval clamps. Air is displaced by blood returning to the right side of the heart.

After left atriotomy or aortotomy, the right ventricular pump is used in a similar way to drive blood through the lungs to the left side of the heart to eliminate entrained air. When the heart has been repaired, the cannulae replaced, and all vascular and line clamps have been removed, the pumps are restarted. The patient is then rewarmed.

Rewarming

The heart is usually in asystole or beating very slowly during circulatory arrest. It may resume normal rhythm or its ventricles may fibrillate with spontaneous recovery later on. Sometimes it is necessary to defibrillate the heart electrically when the temperature has risen to 30°–33°C. This occurs most commonly in adult patients with severe myocardial strain and particularly in patients aged over 45 years with aortic stenosis. Rewarming is continued until a nasopharyngeal temperature of at least 33°C. has been reached and the muscle temperature is about 30°C. The pumps are gradually slowed. Partial right ventricular by-pass is stopped and the cannulae removed from the right side of the heart. Finally, partial left ventricular by-pass is suspended and the cannulae removed from the left atrium and femoral artery. The recording arterial catheter is also withdrawn and the vessels repaired. Protamine or Polybrene is given to neutralize the effect of heparin. Careful haemostasis is carried out before the pericardium is loosely repaired and the chest is closed. Large-bore drainage tubes are used to drain the pericardial space and the anterior mediastinum.

During rewarming, warm water is passed through a blanket placed under the patient. This helps to maintain body temperature while the chest is being closed. In the experimental laboratory surface cooling and rewarming by immersion was used during perfusion. There was no marked difference in the speed of heat exchange and there seemed no justification for the extra apparatus.

The use of a heat exchanger in the extracorporeal part of the pulmonary circulation does not appear to be worth while because the amount of heat transfer in the lungs must be small. These organs would rapidly cool below the temperature of the rest of the body which is probably unwise. Such additional aids may be necessary if in the future it is thought desirable to cool patients nearer 0°C.

a blood path with water on each side. There are single inlets and exits each for blood and water. The blood path is divided into four helical streams, with entry ports designed to maintain even distribution over the heat exchange area. The heat exchanger is made of stainless steel, is easy to clean, assemble, and render free of air. Although it has a priming volume of only 450 millilitres it has a heat exchange area of 5 square feet, equivalent to 16 tubes in the simple apparatus previously described. On the few occasions when it has been used it has proved to be a simple and highly efficient instrument. Not only is it likely to be useful in clinical work requiring hypothermia to 15°C. but it should allow rapid cooling to much lower temperatures in big adult patients.

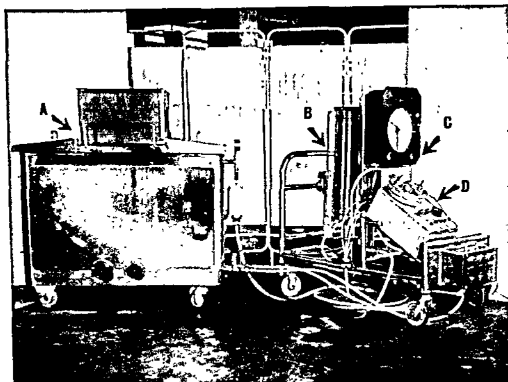


FIG. 50.—Artificial heart and heat exchanger with controlled chilled and warm water circuit. (A) Apparatus supplying water at any temperature between 2°C. and 42°C. (B) Annulus type heat exchanger. (C) Temperature control panel. (D) One of two pumps placed side by side. (The reservoirs are situated on the far side of the trolley and are not visible.)

Conclusion

If further experience confirms the belief that profound hypothermia with circulatory arrest is safe, it is possible that lower temperatures will be used in an endeavour to take advantage of longer periods of suspended animation. This will demand the design of a more efficient method of heat exchange.

At the present time it is impossible to forecast the period of circulatory arrest at different temperatures which is compatible with full recovery.

required for profound cooling is slightly different but no more difficult than that for cardio-pulmonary by-pass. Once the patient is cooled, the pumps stopped, and the heart drained of blood, it is possible to perform the intracardiac surgery as easily as on the cadaver. At this stage the surgeon is independent of a machine. The heart is stopped or beating infrequently and is protected from anoxic changes by its own low temperature. The heart chambers are dry because there is neither continuous myocardial nor bronchial venous return. This allows easy assessment of any abnormality and an accurate repair.

Using a heart-lung machine at normal body temperature, myocardial and bronchial blood needs continuous aspiration. Even if cardiac arrest is induced with potassium citrate or merely by clamping the aorta above the coronary arteries, bronchial venous return can still be troublesome particularly in cases of Fallot's tetralogy. Moreover, the myocardium may become damaged by anoxia if coronary circulatory arrest is prolonged. This is of particular importance in older patients with calcified aortic stenosis, in whom the failing left ventricle is particularly sensitive to anoxia. As the patient's own lungs are used for oxygenation the perfusion flow is only dependent on the output of the pumps and the size of the cannulae.

In practice a high flow is used even during cooling, to facilitate heat exchange, although this is not necessary for the metabolic requirements of the body. The flow in infants has been as high as 150 millilitres per kilogram per minute and in a heavy adult a total flow of 5 litres per minute has been obtained. It is sometimes necessary to use such high flows in moments of cardiac crisis. The heart of Fallot's tetralogy may develop ventricular fibrillation early in the operation before cooling has commenced. It is then necessary to use a high flow to satisfy metabolic demands until the temperature falls. After surgery on a calcified aortic valve, the heart may not respond satisfactorily until rewarming is far advanced. A flow appropriate to a body temperature of 34°C. may be necessary until such time as the heart action is restored. High perfusion flows are more easily obtained in a system which uses the patient's lungs than in one which is dependent upon the efficiency of an artificial oxygenator. One obvious disadvantage is the time taken in cooling and rewarming, but this will become less with increase in our knowledge of heat exchange and the design of a more efficient heat exchanger.

FUTURE DEVELOPMENT

A new type of heat exchanger with a controlled chilled and warm water circuit

A new apparatus developed with the enthusiastic co-operation of the A.P.V. Company and designed by Mr. David Shore is shown in Fig. 50. Outside the operating theatre, a cabinet (A) containing refrigeration and heating units, delivers water to the heat exchanger at any desired temperature between 2°C. and 42°C. A mobile trolley standing by the operating table holds a pair of roller pumps (D), the reservoirs, an annulus type heat exchanger (B), and a combined temperature control panel and time clock (C). The latter is used to regulate the temperature of water passing through the heat exchanger and makes a continuous pen recording of the changes. The heat exchanger consists of concentric cylinders enclosing

Pulmonary stenosis

Valvotomy

Valvotomy as a cure for simple pulmonary stenosis is discussed by CAMPBELL (1959). He describes a group of 64 patients of which 21 had cyanosis and 43 had not: these were survivors from 76 operated upon between 1948–56. In most of the cases the right ventricular pressure exceeded 100 millimetres of mercury and no great difference between the two groups was seen. In most, operation was done through the ventricles but a few were open operations under hypothermia. Twelve of the 76 cases died quickly but some had been gravely ill and congested. Apart from true infundibular stenosis the much hypertrophied muscle of the ventricle may produce similar trouble. Symptoms were absent in about half the acyanotic cases but usual in the cyanotic. Only one of the acyanotic cases did not improve, bundle branch block continued after the operation and the heart became larger. A reduction of the systolic gradient over the pulmonary valve was nevertheless usual, in many cases to under 40 millimetres. Good results occurred in 25 and less good in 14 of the acyanotic cases. In some a degree of pulmonary reflux developed. It did seem evident that age was an important factor in qualifying the improvement which occurred, no doubt because with age the outflow passages were more rigid and the myocardial changes more fixed. It is evident that the operative results are more easily judged with the cyanotic cases and in this series all improved clinically and only two had residual cyanosis. In the whole group average arterial oxygen saturation rose from 78 to 94 per cent and the pulmonary flow from 2·5 to 4·2 litres. Associated with this the polycythaemia and the haemoglobin percentages fell to normal. In 10 of the cyanotic cases some degree of pulmonary stenosis remained but probably with little handicap therefrom. In 57 patients examined no marked T-wave inversion remained in 37. The changes in R : V preponderance were not very striking, though they were in the direction expected. The average height of the R wave in V1 was reduced to a third or less, when results were good clinically. The rate of improvement varies. Temporary post-operative changes, such as T-wave inversion may develop or increase soon after operation but, if readings are taken after a year, a suitable time, then those associated with greater clinical normality are often found. Even so improvement may last for two or three years, as measured by electrocardiogram. In the writer's opinion a systolic gradient of 50 millimetres across the valve is an indication for operation. It is stressed that studies of such cases should continue for many years to increase our knowledge in this field.

Atrial septal defect, secundum

Open surgical repair

SWAN and his colleagues (1959) surveyed a series of 100 cases of interatrial septal defect of the secundum variety. The age span of the series ranged from 10 months to 45 years. Dyspnoea and fatigue were prominent symptoms in many cases, but 38 patients were essentially asymptomatic. A history of pulmonary infection was obtained in 31 cases. Most patients were underweight with reference to their height. Precordial bulging was often found and the lift of the pulmonary artery expansion as well as the shock of closure of the pulmonary valve could usually be palpated. A systolic thrill was present in 7 cases. On auscultation, a systolic murmur was invariably heard. The murmur was maximal in either the second or third left intercostal space. In 51 cases a short diastolic murmur was detected towards the apex or at the left edge of the lower part of the sternum. Lutembacher's syndrome was not observed. The second sound at the cardiac base was widely split except in patients with high pulmonary vascular resistance. Abnormal electrocardiographic findings were related to the extent of right-sided hypertrophy. Enlargement of the heart was confirmed on fluoroscopy. Surgery was employed in all cases and 92 patients survived with increase in weight, strength and energy. Subsequently the precordium showed less activity, the systolic thrill disappeared and the systolic murmur diminished in intensity. Usually the second cardiac sound and the electrocardiographic tracings changed to normal. Cardiac catheterization revealed a reduction

Experience could in time answer this question but it may be possible to predict it by more complete studies of oxygen consumption during cooling and rewarming. Indeed, if such measurements could be continuously monitored they might be more reliable than temperature recordings.

It is possible that cooling with suspended animation may find a place in other fields of surgery in which intervention is now contra-indicated or dangerous. This may be due either to the fear of haemorrhage or to the knowledge that even temporary occlusion of its blood supply at normal body temperature may lead to death in a vital organ.

REFERENCES

Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gordon, R. A., and Greenwood, W. F. (1950). *Amer. J. Physiol.*, **160**, 125.
Drew, C. E., and Anderson, I. M. (1959). *Lancet*, **1**, 748.
— Keen, G., and Benazon, D. B. (1959). *Ibid.*, **1**, 745.
Lewis, F. J., and Taufic, M. (1953). *Surgery*, **33**, 52.

SELECTED ABSTRACTS

Surgical treatment of mitral stenosis

Transventricular approach with mechanical dilator

Logan and Turner (1959) discussed the surgical treatment of mitral stenosis, with particular reference to the transventricular approach with a mechanical dilator. At operation, when the valve must be palpated through an atrial approach, the commissures frequently cannot be recognized accurately. Although digital valvulotomy does not primarily require accurate localization of the commissures, accurate knowledge of their position and direction is a theoretical pre-requisite for the use of a knife. As a result of failures with the standard techniques the authors decided to approach the mitral valve from the ventricle and to guide the instrument into position by transatrial palpation; the dilator used has been one with a spread of 5 centimetres. The use of the transventricular dilator necessitates an exposure of the left ventricle only slightly better than that provided by thoracotomy for the transatrial technique: if a gentle attempt at digital valvulotomy fails, the ventricle is incised near the apex, and the head of the dilator is accurately placed in the valve orifice under the guidance of the atrial finger. The use of the dilator must be abandoned if one commissure is completely divided while the other remains intact, or if neither gives way with the use of moderate force. A comparison of valvulotomy before and after the dilator came into use can be made by: technical advantages and disadvantages; the extent of commissural division; incidence and severity of traumatic mitral incompetence; incidence and cause of operative and early post-operative death. Although length of survival, duration of improvement, or need for re-operation, cannot yet be compared, there is some reason to believe that eventually comparison will be satisfactory. The method has been used in the treatment of 438 patients, and the results show that the use of the dilator was associated with a marked increase in the incidence of complete anterior and posterior commissural division, and a decrease in incomplete division of both commissures. The operative mortality has been 5 per cent compared with 6·6 per cent, and a greater number of patients have been improved. The technique has produced good results in a surprisingly high proportion of cases with heavy calcification of the valves. Although there have not been more deaths from traumatic mitral incompetence than with other methods, there has been, with improved commissural division, a slightly higher incidence of post-operative systolic murmurs. The authors conclude that prediction of the results of operation cannot be achieved by pre-operative examination.

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Atrial septal defect, secundum

Open surgical repair

SWAN and his colleagues (1959) surveyed a series of 100 cases of interatrial septal defect of the secundum variety. The age span of the series ranged from 10 months to 45 years. Dyspnoea and fatigue were prominent symptoms in many cases, but 38 patients were essentially asymptomatic. A history of pulmonary infection was obtained in 31 cases. Most patients were underweight with reference to their height. Precordial bulging was often found and the lift of the pulmonary artery expansion as well as the shock of closure of the pulmonary valve could usually be palpated. A systolic thrill was present in 7 cases. On auscultation, a systolic murmur was invariably heard. The murmur was maximal in either the second or third left intercostal space. In 51 cases a short diastolic murmur was detected towards the apex or at the left edge of the lower part of the sternum. Lutembacher's syndrome was not observed. The second sound at the cardiac base was widely split except in patients with high pulmonary vascular resistance. Abnormal electrocardiographic findings were related to the extent of right-sided hypertrophy. Enlargement of the heart was confirmed on fluoroscopy. Surgery was employed in all cases and 92 patients survived with increase in weight, strength and energy. Subsequently the precordium showed less activity, the systolic thrill disappeared and the systolic murmur diminished in intensity. Usually the second cardiac sound and the electrocardiographic tracings changed to normal. Cardiac catheterization revealed a reduction

in pulmonary-artery pressure. As for surgical technique, the operation is performed under hypothermia. The authors recommend a bilateral trans-sternal thoracotomy in the fourth intercostal space. Search is made for other anomalies such as patent ductus arteriosus. Tapes are passed loosely around the venae cavae and an incision is made in the right atrium distal to a clamp applied to the wall. The tapes are tightened and the heart allowed to empty itself. A solution of neostigmine is injected between a clamp placed on the aorta and the coronary arteries to reduce the heart rate. The clamp is removed from the right atrial wall, blood removed from the heart by suction and the septal defect repaired. Air is displaced from the heart by allowing it to fill with blood from the cavae before the atrial clamp is replaced. The aortic clamp and caval tapes are then removed and the heart resumes its normal beat. Circulatory occlusion is limited to six minutes. Details are given of the surgical technique required to deal with anomalous pulmonary venous drainage.

Anomalous pulmonary venous drainage

Cooley and Collins (1959) reported on the surgical treatment of seven cases of anomalous pulmonary venous drainage into the innominate vein. In the first case, an infant aged one month, the vertical anomalous vein was anastomosed to the left atrial appendage and partial ligation of the vertical vein was performed. The infant died four hours later. A similar result was recorded in an infant aged two months. The third patient was a man, aged 40 years, with cyanosis, cardiac failure and severe cardiomegaly, hepatomegaly and pulmonary oedema. The patient died during the preliminary exploration. In view of this experience cannulation of the venae cavae was employed in the remaining cases. The venous outflow was connected to a pump oxygenator and the common femoral artery was intubated for the return of oxygenated blood. Complete correction was effected during cardio-pulmonary by-pass and the results were excellent. With regard to the technique of repair, the right atrium was opened, the atrial communication was identified and the septum was detached from the atrial wall. After posterior atriotomy an anastomosis was effected with the venous trunk. The septum was transposed ventrally and special sutures were inserted in order to increase the size of the left atrial cavity. The right atriotomy was closed and the vertical anomalous vein was ligated. Two clinical patterns are described. Whereas in infants symptoms are due to congestive heart failure, in older children the characteristic manifestations are exertional dyspnoea and cyanosis. Variations in the findings depend upon the magnitude of the right-to-left shunt at the atrial level. As for the radiological appearances, a figure 8 configuration of the mediastinum is almost pathognomonic of the anomaly. The upper half of the figure is formed by the vertical anomalous vein on the left and the prominence of the superior vena cava. This pattern is not observed in infants.

Simultaneous repair of mitral and tricuspid valves

Julian and his colleagues (1959) described simultaneous repair of mitral and tricuspid valves through the right atrium and interatrial septum. Secondary tricuspid regurgitation often leads to clinical deterioration in patients whose only rheumatic valvular lesion is mitral. Tricuspid sufficiency appears to result as a more or less delayed benefit of mitral valve commissurotomy or repair, suggesting that a combined operation would provide more rapid and certain improvement in cardiac competency. An open approach is advocated. In this series, eight patients were subjected to a tricuspid-annulus-plication procedure simultaneously with operation on the mitral valve. In every case tricuspid insufficiency was severe and did not remit during medical treatment. In three patients, the mitral lesion was insufficiency; in two, stenosis; in three, stenosis and insufficiency. The accepted incision and approach to the mitral valve, through a right thoracotomy for left atriotomy, was used in seven cases. To carry out simultaneous tricuspid repair, the approach was made through the lateral wall of the right atrium, with subsequent exposure of the mitral valve through an incision in the interatrial septum. This is a more accessible route than that through the left atrial wall. In the eighth case, incision was

through a median sternotomy. Potassium cardiac arrest was induced in every case by rapid injection of a 2·5 per cent solution in blood of potassium citrate into the root of the aorta, proximal to an occluding clamp placed after balanced cardiopulmonary by-pass had been established. This provides a quiet operative field and permits of easy retraction and rotation of the heart if necessary. The extracorporeal circuit consisted of a bubble-diffusion oxygenator. Blood was removed from the superior and inferior venae cavae by pumping. Both femoral arteries were cannulated. Repair was carried out under total cardiopulmonary by-pass. Plication of the annulus of the tricuspid valve was done in every case. Either direct-vision commissurotomy or annulus plication was performed on the mitral valve. The procedure is described. Two operative and two late surgical deaths occurred in this series of poor-risk patients. In the surviving four, changes in liver size and pulsation, venous pressure and pulsation and softening or disappearance of the murmurs are the most encouraging features. Patients, however, should be selected and those with severe pulmonary vascular changes secondary to long-standing heart disease should be excluded.

Surgical treatment of aortic insufficiency

Chronic experimental studies

GARAMELLA and his colleagues (1959) discussed experimental studies following the surgical treatment of aortic insufficiency by conversion of the tricuspid aortic valve to a bicuspid valve. Eleven chronic survivors of this procedure were studied 26–405 days post-operatively. The animals were anaesthetized with intravenous thiamylal sodium, 75–100 milligrams. A No. 18 gauge needle was inserted percutaneously into the femoral artery. Through a No. 13 to 15 gauge needle, passed into the left ventricle at the point of maximal impulse, a polythene catheter was threaded, passing through the bicuspid valve into the central aorta. Connexions were made to Statham strain gauges P23A and a Sanborn Poly-Viso recorder. Analyses of femoral artery pulse curves showed dicrotic notches in 10 cases. Several animals demonstrated broadened pulse pressures. No significant changes in the duration of systolic ejection phases were found. Continuous pressure recordings from the central aorta to the left ventricle showed a minor systolic gradient in four cases; end diastolic pressures were slightly raised in two. Results show that dogs tolerate plastic conversion of the aortic tricuspid to a bicuspid valve. Pathological studies support this concept for clinical application. More recent work demonstrates first, that in rheumatic aortic valvular insufficiency, the non-coronary cusp appears to interfere with the coaptation of all three cusps and therefore contributes to regurgitation; secondly, that the reconstructed bicuspid valve coapts well and minimizes regurgitation. The method involves total excision of the non-coronary aortic cusp with a corresponding triangular segment of the base of the aorta. By suture repair, a bicuspid valve is produced and the aortic circumference reduced by one-third.

Closure of cardiac defects

Use of atrial grafts

FITZPATRICK and his colleagues (1959) reviewed the use of atrial grafts for the closure of cardiac defects. These include atrial septal and ventricular septal abnormalities, atrioventricularis communis, infundibular stenosis and certain acquired lesions. The materials used range from homologous and autogenous grafts to plastics, including polyethylene and Ivalon. The disadvantages of plastics, however, within the heart led to this study of autogenous atrial grafts. Thirty mongrel dogs were anaesthetized, the pericardium opened and the right or left atrial appendage amputated. In 12 dogs, the appendage was resutured to the atrial wall; in the remainder, the free portion in its entire thickness was trimmed to close artificially created defects in the atrial septum, right ventricle or opposite atrium. The animals were killed at various intervals; the ascending aorta was opened and the right and left main-stem coronary arteries securely cannulated. Both coronaries were then injected with a Vinylite-lead mixture after removal of the pericardium. The graft area of the heart was excised with adjacent normal myocardium

and x-rays were obtained. Histological specimens were taken. No disruption or necrosis of the graft occurred in any dog. These autologous grafts with their fat cells and connective tissue remain viable, while muscle replacement gradually occurs. They are traversed by blood vessels across the suture line as early as seven days after application. Thrombosis formation occurs at the surface which is re-endothelized by the third week. Atrial grafts are firm and tough, unlikely to undergo aneurysmal dilatation and produce no foreign body reaction.

Thoracic vascular surgery

Changing concepts

Discussing thoracic vascular surgery, De Bakey (1959) stated that although removal of the lesion and restoration of vascular continuity are the primary objectives of therapy certain modifications require consideration. For instance, partial excision and endoaneurysmorrhaphy may suffice for the treatment of some types of aneurysm. Removal of the lesion is not always essential in cases of occlusive disease. When a relatively long coarcted segment extends into the abdominal aorta or when an occlusive lesion affects the major branches of the aortic arch use of a by-pass graft may avoid the hazards associated with excision and graft replacement. In the management of most aortic aneurysms in which the proximal occluding clamp can be applied distal to the left common carotid artery a pump by-pass provides adequate circulation. Oxygenated blood is removed from the left auricle and pumped through a cannula inserted into the left femoral artery. The technique is not completely effective in preventing spinal cord damage, for this complication was encountered in 2 of 55 cases in which the technique was employed. Unless the lesion is situated in the proximal 3 or 4 centimetres of the ascending aorta, the temporary by-pass principle is adopted for aneurysms of the aortic arch proximal to the level of the left common carotid artery. So far as the carotid arteries are concerned, the temporary internal shunt principle may be adopted if technical difficulties are likely to arise from end-to-side anastomosis and the use of a partial occluding clamp. A temporary by-pass graft may be converted into a permanent graft by means of a Dacron tube. For aneurysms of the proximal segment of the ascending aorta it is necessary to employ the cardio-pulmonary by-pass technique and the artificial heart-lung apparatus. Operative risks may be related to advancing age, hypertension and associated heart disease. Thus the operative fatality rate for fusiform aneurysms of the descending thoracic arch is three times greater in patients in the seventh and eighth decades of life than in younger patients. As the margin of safety in this field of surgery is often small much depends upon attention to details and dexterity in technical performance.

Antiheparin potency of polybrene and protamine

Patients undergoing extracorporeal circulation

Keats, Cooley and Telford (1959) discussed the relative antiheparin potency of polybrene and protamine in patients undergoing extracorporeal circulation. Forty non-cyanotic patients, including children and adults, with various cardiac diseases were studied. Clotting times were determined by the Lee-White method. All samples of blood, collected from the right ventricle, were drawn: (1) prior to heparinization, 20 minutes before cardiopulmonary by-pass; (2) 5 minutes after heparinization; (3) 5 minutes after administration of the heparin antagonist and approximately 10 minutes after cardiopulmonary by-pass; (4) 15 minutes after administration of the antagonist; (5) 5 minutes after administration of additional antagonist in some patients. Various doses of both antagonists were studied; these were injected undiluted over a period of 30–60 seconds. The time elapsing between administration of heparin and antagonists was 30–40 minutes. In all patients, heparin (1·5 milligrams per kilogram body weight) prolonged coagulation time by more than 60 minutes beyond the control (pre-heparin) clotting time. Comparison of heparin neutralization by both drugs, 5 and 15 minutes after administration, showed that the maximum antiheparin effect occurred within 5 minutes and that polybrene was 1·5 times as potent as protamine at 100 per cent

neutralization. Further data, obtained by giving additional doses of polybrene to patients whose clotting times did not return to control values after the additional antagonist dose, confirmed these findings. Among the 40 patients, no marked hypotension occurred following the rapid administration of either drug at any dose level. Side-effects were studied in 11 adult patients recovering from minor surgical procedures. Intravenous undiluted protamine (5 milligrams per kilogram body weight) or polybrene (3 milligrams per kilogram body weight) was injected rapidly over a period of 30–60 seconds. Neither drug produced any significant change, although protamine tended to have the greater hypotensive effect. No alarming reaction occurred in any patient, either anaesthetized or conscious. Subjective effects produced by both drugs at twice the heparin neutralization were mild and transient.

Edglugate-Mg

Donor blood anticoagulant—preservative mixture

Smith and his colleagues (1959) point out that heparin is a poor anticoagulant for preserving donor blood for any length of time. Within 12–30 hours of storage blood collected in heparin usually becomes unfit for perfusion. On the other hand, when Edglugate-Mg solution is added to donor blood the mixture is suitable for extracorporeal perfusion for as long as five days after storage. For ordinary transfusion the blood may be used for periods up to 21 days of storage. Sodium gluconate is added in order to preserve the red blood cells. If glucose is employed instead of sodium gluconate slight haemolysis may take place during the second and third weeks of storage. Prior to use commercial heparin, 15 milligrams, and a sterile aqueous solution of calcium chloride, 5 millilitres, are added to 500 millilitres of the blood. Calcium chloride is added in order to offset the effect of the increase in the level of plasma potassium. No difficulties were encountered in 81 perfusion cases in which the extracorporeal apparatus was primed with Edglugate-Mg blood stored for periods not exceeding five days. All patients were perfused under hypothermia. No bleeding attributable to thrombopenia and no purpuric manifestations were encountered despite the fact that the platelets had lost their haemostatic function after two days' storage. The incidence of transfusion reactions resembled the reaction rates encountered with citrated blood. It is noteworthy, however, that increase in the potassium content of the plasma and depression of the antihaemophilic globulin and Factor V levels were detected when the storage period was longer than five days.

REFERENCES

Campbell, M. (1959). *Brit. Heart J.*, **21**, 415.
Cooley, D. A., and Collins, H. A. (1959). *Circulation*, **19**, 486.
De Bakey, M. E. (1959). *J. thorac. Surg.*, **38**, 145.
Fitzpatrick, H. F., Bossart, P. A., Grunwald, R. P., and Zintel, H. A. (1959). *Arch. Surg.*, **78**, 212.
Garamella, J. J., Andersen, J. G., Oropeza, R., Velosa, A., and Naidu, R. (1959). *J. thorac. Surg.*, **37**, 177.
Julian, O. C., Lopez-Belio, M., Dye, W. S., Javid, H., Prec, O., Sa'd El Issa, and Lima, A. (1959). *Arch. Surg.*, **78**, 745.
Keats, A. S., Cooley, D. A., and Telford, Jane (1959). *J. thorac. Surg.*, **38**, 362.
Logan, A., and Turner, R. (1959). *Lancet*, **2**, 874.
Smith, W. W., Brown, I. W., Young, W. G. Jnr., and Sealy, W. C. (1959). *J. thorac. Surg.*, **38**, 573.
Swan, H., Kortz, A. B., Davies, D. H., and Blount, S. G. Jnr. (1959). *J. thorac. Surg.*, **37**, 52.

URINARY TUBERCULOSIS

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INTRODUCTION

During recent years the general incidence of tuberculosis has been considerably reduced, while infection with the bovine type of bacillus is now a distinct rarity. Nevertheless, if left untreated the disease is the same as it ever was. A primary focus, if not rapidly overcome by the local tissue defences, is followed by a blood borne dissemination, and when this occurs, both kidneys are inevitably involved. The fact that a clinical lesion may only manifest itself in one kidney does not alter this thesis: the disease is potentially bilateral, and over one-quarter of the renal patients admitted to Harefield Sanatorium during the past eight years had already undergone a nephrectomy for so-called unilateral disease during the previous 5–15 years.

Tissue reaction and healing

The normal tissue reaction to the tubercle bacillus consists of an attempt to surround the organism by leucocytes and to confine the whole area in an avascular fibrous capsule. If the first attempt at confinement fails, the lesion bursts out of this capsule, only to be surrounded by a further layer of fibrous tissue. This process, though it protects the host as a whole from a further blood stream dissemination, causes progressive local tissue destruction. When a balance of power is established we are left with an avascular caseating area, perhaps containing active tubercle bacilli firmly surrounded by a thick fibrous capsule. This may be quiescent, but it is hardly "cured".

However, the classical picture of a steadily progressive destructive disease is now becoming a rarity, because modern drug therapy, by killing or weakening the tubercle bacillus, allows the normal tissue defences to act more efficiently and we are witnessing, for the first time, the processes of rapid healing in tuberculosis. Healing, however, consists of the halting of the destructive process, and not the regeneration of already destroyed tissue. Thus, even when the lesion is "cured" the patient will not possess any more renal parenchyma than was present when the treatment was first commenced, so that early diagnosis is obviously of prime importance.

Healing also creates certain problems of its own. It is largely achieved by fibrosis, and the pathological and mechanical changes which occur as a result of this protective fibrosis are of vital importance to the urologist.

Radiology

An important fact which we have to accept is that a healed lesion may present a very bizarre radiographic appearance and it is quite impossible to decide whether such a lesion is progressive or quiescent without repeated radiological studies. In fact it is dangerous to prescribe intensive drug therapy unless such constant supervision is available.

In the past the value of radiology was largely confined to the initial diagnosis, because the localization of a small tuberculous focus in a kidney was a cue for immediate nephrectomy, but today radiology also plays a vital role in the treatment. The whole management of a case is dictated by the mechanical changes which occur as a result of the healing fibrosis, and these can only be assessed by repeated radiological studies over a period of months.

GENERAL PRINCIPLES OF MODERN THERAPY

Genito-urinary tuberculosis can now be controlled by conservative drug therapy provided that the following conditions are fulfilled:

(1) The bacillus is sensitive to all of the drugs prescribed, and that these are actually taken by the patient in adequate doses for a continuously long period of time.

(2) The blood supply to the lesion is adequate.

(3) There is no urinary obstruction.

The urine should be free from tubercle bacilli within three months of the commencement of adequate drug therapy. If this does not occur a search should be made for some error in management. Either the organism is resistant to one of the drugs (in our experience this is extremely rare unless the patient has received previous drug treatment) or there is a semi-closed caseating area with a poor blood supply, or—most important of all—the patient is not taking the drugs as prescribed.

Principles of drug therapy

It cannot be repeated too often that drug therapy must not be started until the diagnosis has been confirmed by isolating the tubercle bacillus on culture or by guinea-pig inoculation. A positive Ziehl-Neelsen stained film is not enough. The notion that a few weeks' treatment pending confirmation of the bacteriology will benefit the patient can be frankly dangerous. At Harefield Hospital drug treatment is not commenced until the culture or guinea-pig results have been reported to us by the referring hospital or clinic. If such tests have not already been set in motion, we may have to wait 6–8 weeks for our own cultures to incubate.

Every patient on admission has three consecutive early morning specimens of urine set up for culture. If the diagnosis has already been established, treatment is then commenced, and it is our experience that over 50 per cent of the patients will have a tubercle-free urine after two months' intensive therapy; that is to say, the cultures reported upon at the end of four months will be negative. The implications of this are obvious. Once drug treatment has been started there may never be a further positive culture or guinea-pig report. In the pre-clinical renal lesions which have merely presented with an early "cystitis", diagnostic radiographic changes may be absent while even the bladder symptoms may be completely relieved by a

very short course of drugs. In such cases one cannot make or refute the diagnosis in the absence of a previous culture report. Two courses of action are therefore open for consideration: to stop treatment immediately and wait and see what happens, or to continue treatment as if the diagnosis had been confirmed beyond doubt. If treatment is continued it must not be half-hearted and should probably be continued for up to two years, because, should a relapse occur, these are the patients who develop resistant organisms, and this can be a tragedy.

If one stops treatment it may be six months before tubercle bacilli are detected once more. Again these bacilli may now be resistant strains. It is obvious that this uncertainty is better avoided than overcome, so that no drugs should be given until tubercle bacilli have been isolated. The only exception to this rule can be a positive declaration by a pathologist reporting on a biopsy section.

ANTITUBERCULOUS DRUGS

The three most important drugs in common use are streptomycin, isonicotinic acid hydrazide (INAH) and para-aminosalicyclic acid (PAS). None of these drugs should ever be administered separately.

The best results at Harefield have followed the use of all three drugs for prolonged periods without interruption, in doses of 1 gramme streptomycin daily, 400 milligrams INAH daily, and 15 grammes or more of PAS daily. We have attempted to maintain this regimen until the urine has been sterile for six months, after which a modified ambulatory regimen is continued for up to two more years. When this ideal has been possible there have been no subsequent relapses, while resistant strains of bacilli have not occurred. In fact, no resistant strains of tubercle bacilli have developed in any patient treated in Harefield Hospital from the outset.

It must be clearly understood that this regimen is our ideal but cannot always be carried out. The first signs of eighth nerve involvement will call for the abandonment of streptomycin, while there are some patients who just cannot take PAS in any form.

Skin reactions can generally be overcome by suitable desensitization and have not been a problem at Harefield. Fortunately INAH is a very powerful antituberculous drug and is non-toxic in most cases, so that in only a very few instances has it not been possible to use a combination of at least two of the three standard drugs for long periods. When possible this sanatorium regimen is continued until the urine has been sterile for six months, during which time the indications for surgery are carefully and constantly studied. Co-existing pulmonary, or bone and joint disease, or both, are cared for by the respective clinicians, but the principles of drug treatment already given are acceptable to all of the specialities. It may be argued that when all evidence of active disease is removed by, say, a nephrectomy, there is no need for prolonged drug treatment. However, tuberculosis is potentially bilateral, and although the period of stay in hospital can be reduced, the ambulatory treatment must be continued for two years as before.

AMBULATORY TREATMENT

When the disease has been stabilized the patient should be encouraged to return home to work—not as an invalid, but as a normal member of the family and

community—but should continue with a modified drug regimen until the urine has been sterile for about two years. It has not been found necessary to continue with streptomycin provided the patient can, and will, take INAH (400 milligrams daily) combined with PAS. No rest periods are allowed, and urine cultures are controlled every three months.

URINE EXAMINATIONS

A positive Ziehl-Neelsen stained slide must never be accepted as proving the existence of a tubercle bacillus. Guinea-pig inoculation is still the final court of appeal, and all doubtful Löwenstein cultures must be confirmed by this means. However, the introduction of drug therapy has necessitated a vastly increased number of urine examinations, and the use of guinea-pigs for each such investigation is usually impracticable when dealing with large numbers of patients. Fortunately a laboratory which is experienced in this work can achieve almost the same degree of accuracy with their cultures as with guinea-pig inoculation, so that today a majority of urines are tested by culture, the guinea-pig being reserved for confirmation of doubtful organisms. Whether a guinea-pig or culture is used, the greatest degree of accuracy will result when the urine is free from secondary organisms. In other words the urine must be as fresh and uncontaminated as possible, and this completely rules out the use of a 24-hour specimen.

The routine employed in the Genito-urinary Unit at Harefield Hospital is as follows.

Three early morning urines are cultured every month without stopping drug treatment. It is possible to train most female patients to collect cleanly their own midstream specimens of urine, particularly if it is explained that this will save catheterization. In the early stages of treatment it is a wise precaution to culture a sample of these urines for ordinary pathogens in order to avoid the delay and disappointment of a contaminated Löwenstein culture. In both sexes, where the urine is moderately infected a short five-day course of Gantrisin prior to the collection of the early morning specimens has been of great value in reducing the number of contaminated cultures. Every positive culture should automatically be tested for sensitivity to all of the drugs used, while a persistently positive urine can only be regarded as a failure of management. There must be a reason for the failure.

INSTITUTIONAL VERSUS AMBULATORY TREATMENT

It would seem impossible to prove that bed rest is essential during the drug treatment of genito-urinary tuberculosis, therefore it can be argued that ambulatory treatment, or even treatment carried out at home, is perfectly adequate. Under ideal conditions this would undoubtedly be so, but in practice these ideal conditions seem impossible to attain as an out-patient, largely on psychological grounds. Unless the patient is incarcerated in an institution at the commencement of his treatment, it does not appear possible for him to acquire the correct mental and physical discipline necessary to face the prospect of two or more years of intensive drug therapy and repeated urological investigations. Whether he is retained in a

general ward or in a special ward should be largely immaterial, but in our own experience the advantages of a preliminary stay in a special ward in a sanatorium have been overwhelming. The difference, we believe, is due entirely to psychological effects. The patient has around him other people who have the same problems at their work, at home, or with their length of treatment. Other people have to take the unpleasant PAS and put up with injections, therefore self pity is minimized.

Should a patient develop drug reactions these can only be overcome in a specialized unit where previous experience of desensitization can be applied. Patients are constantly being admitted to Harefield largely because they "cannot take antituberculous drugs". Obviously they are not responding to treatment and they not infrequently have resistant organisms. With patience and sympathy these problems can nearly always be overcome, but only in a unit used to such work. This is "nursing" at its best. Once a patient has accepted the dull routine of his treatment during a few months in hospital, there is very rarely any difficulty in continuing the ambulatory treatment when he returns home to work, but these few initial months of discipline while the disease is being stabilized are a very important part of this therapy.

INDICATIONS FOR SURGERY

It was originally thought that with the introduction of really effective antituberculous drugs, the need for surgery would disappear. Certainly the need for radical surgery has almost disappeared, but it has been replaced by conservative and reparative surgery which has become more stimulating and challenging and requires much greater patience and clinical acumen than a rule of thumb nephrectomy. The fact that tuberculosis heals by fibrosis presents special problems to the urologist who is already concerned with anatomically narrow tubes. When a lesion becomes sealed off by protective fibrosis the urine may become free from tubercle bacilli, but this should not lull one into a false sense of security. Such a lesion is by no means healed, and it is to be hoped that it will subsequently break down and drain away into the pelvis and ureter.

The principles of surgery in renal tuberculosis are therefore the maintenance or provision of drainage and the evacuation of caseous material.

THE CALYX

The first radiologically demonstrable lesion occurs at the tip of the renal papilla (Fig. 51) which becomes eroded or flattened. This is an irreversible process because once tissue is destroyed it cannot be replaced, so that even when the disease is controlled by adequate drug therapy, the calyx will remain "clubbed". However, the ulceration of the calyceal walls will heal during drug therapy, and when they become re-epithelialized the urine will be free from pus cells and albumin, and this is an excellent prognostic sign. Unfortunately all too often, the inflammatory process involves the neck of the calyx causing obstruction. Not only does this urinary back pressure tend to damage the renal segment concerned, but it creates an isolated avascular area which is less accessible to drug therapy. When such a calyx becomes radiologically obliterated we must decide whether this is due to a true stricture at the neck, or whether the cavity is merely filled with caseous material.

Unless there is complete organic narrowing of the neck, caseous material will eventually soften and drain away into the pelvis, so that complete healing can, and generally does, occur. However, when such a cavity is first encountered it is not always possible to tell whether it will reopen or not. Fortunately there is no urgency. A cavity which is not outlined by repeated excretion or retrograde pyelography probably has a permanent stricture, but if the shadow is variable, faint, or irregular, one may hope for eventual drainage and healing. Some of our cases have opened up 6–9 months after the commencement of treatment, and although the radiological appearances of such cavities will always be bizarre, provided there is free drainage and the urine is free from tubercle bacilli there is no indication for surgery.

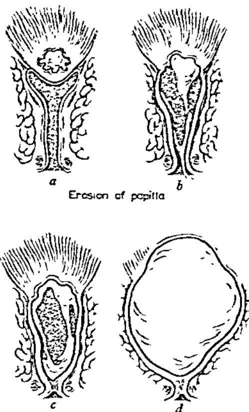


FIG. 51.—(a) Tuberculous focus within papilla; (b) erosion of papilla. Calyx partially filled with caseous material; (c) blockage of the neck of the calyx. In many cases this blockage may only be temporary, in which case the caseous pus drains away leaving a distorted but healing calyx; (d) permanent stenosis of the neck will produce a pyocalyx which may grow into a large avascular abscess, completely separated from the main collecting system.

The true stricture will cause a permanent pyocalyx, and even if this remains cut off from the pelvis, in which case the urine will be sterile, it will be avascular and may be a permanent source of latent infection. Such a closed cavity will probably require surgical drainage.

Partial nephrectomy

This operation, which became possible as a result of the introduction of the antituberculous drugs, has now been rendered unnecessary by their continued use.

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The principles of surgery in renal tuberculosis are therefore the maintenance or provision of drainage and the evacuation of caseous material.

THE CALYX

The first radiologically demonstrable lesion occurs at the tip of the renal papilla (Fig. 51) which becomes eroded or flattened. This is an irreversible process because once tissue is destroyed it cannot be replaced, so that even when the disease is controlled by adequate drug therapy, the calyx will remain "clubbed". However, the ulceration of the calyceal walls will heal during drug therapy, and when they become re-epithelialized the urine will be free from pus cells and albumin, and this is an excellent prognostic sign. Unfortunately all too often, the inflammatory process involves the neck of the calyx causing obstruction. Not only does this urinary back pressure tend to damage the renal segment concerned, but it creates an isolated avascular area which is less accessible to drug therapy. When such a calyx becomes radiologically obliterated we must decide whether this is due to a true stricture at the neck, or whether the cavity is merely filled with caseous material.

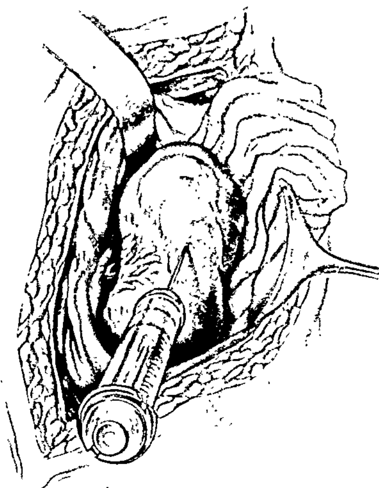


FIG. 54.—Renal cavernotomy. Aspiration of abscess through wide-bore needle. As the roof collapses the walls become clearly defined.

cavities contain living tubercle bacilli, which is not surprising since they are avascular and therefore inaccessible to the blood borne drugs. Their evacuation has invariably resulted in a marked improvement in the patient's general health, with a drop in the erythrocyte sedimentation rate and, in four instances, with a drop in systemic blood pressure.

Such cavities must indeed be completely closed off before a cavernotomy is performed, otherwise a urinary fistula may develop. Quite apart from this, an

Not long ago it was thought desirable to resect an irregular scarred calyx, but it was then found that following adequate drug therapy, many partial nephrectomy specimens showed complete healing and re-epithelialization. Therefore, the accepted view today is that, no matter how distorted the calyx appears, provided it is draining and the urine is free from tubercle bacilli, it can safely be left *in situ*.

Renal cavernotomy

A speliostomy or cavernostomy is not a new operation, but its application to the kidney in a modified form without any drainage or irrigation, that is, a cavernotomy, has recently proved very successful in cases of large completely closed-off abscess cavities (Hanley, 1960).



Fig. 52.—Retrograde pyelogram showing radiological absence of upper and mid-zone calycine system. Space filling lesion full of pus.

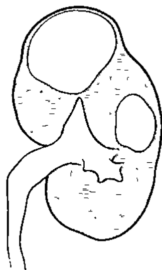


Fig. 53.—Diagram of kidney reconstructed over the pyelogram shadow in Fig. 52 to show the two large cavities drained by cavernotomy.

When a large area of renal tissue remains separated from the main pelvic collecting system, one must assume that there is a space-filling lesion (Fig. 52) consisting of a closed-off abscess. If repeated pyelography fails to outline the cavity and if prolonged antibiotic therapy produces a sterile urine, perhaps even free from pus cells, the cavity is truly sealed off. However, it is our experience that most of these

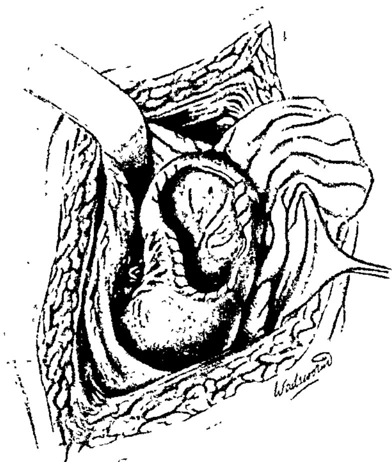


FIG. 56.—Renal cavernotomy. Haemostasis is achieved by oversewing any bleeding points with fine catgut on an atraumatic needle.

The kidney should be exposed through the bed of the twelfth rib, and because the situation of the abscess can be assessed by a careful study of the radiographs (Fig. 53) very little renal mobilization should be necessary.

The abscess, which is clearly visible and palpable, should be aspirated through a wide-bore needle (Fig. 54). As the roof collapses the limits of its walls are accurately defined, so that an avascular area in the centre can be grasped with forceps and opened with scissors. The caseous contents can now be removed gently with dry

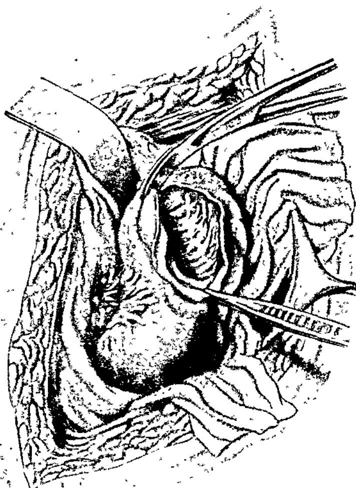


FIG. 55.—Renal cavernotomy. The cavity roof being excised with scissors. Care should be taken to preserve an overhanging edge or troublesome bleeding will occur. The thick caseous lining of the cavity is removed by gentle swabbing with dry gauze.

incompletely sealed-off cavity would probably drain away spontaneously, so that surgery would have been unnecessary.

Operative technique of cavernotomy

The operation is much safer and simpler than a partial nephrectomy and is much more conservative of renal tissue.

film of the series. This is because urine passes through this segment very rapidly and is not normally held up at the uretero-vesical junction. However, minor degrees of bladder or urethral irritation can cause oedema or spasm in this region so that both lower ureters may remain filled (not necessarily dilated) throughout the whole period of a pyelogram investigation. This is a non-specific reaction and is frequently seen in cases of cysto-urethritis, especially in young women. It is transitory and disappears completely when the cysto-urethritis subsides. Such a radiological picture may be one of the earliest signs of renal tuberculosis, particularly in patients whose presenting symptoms are due to bladder and urethral irritation, and is again a non-specific reaction.

Unfortunately it is impossible to tell from one set of pyelogram films whether the ureteric hold-up is due to non-specific oedema and spasm or whether it is due to a true tuberculous process, so that the radiological studies must be repeated after two or three months' drug therapy. By this time the ureters should have returned to normal, but if not great care is necessary, because stricture formation at this site is silent and progressive, and can destroy a kidney by simple back pressure effects more rapidly than the tuberculous disease itself. In fact healing fibrosis may close the lower ureter while the kidney above is responding satisfactorily to treatment. Fortunately, obstruction of the lower ureter if diagnosed early is completely amenable to surgery and there is little excuse for failing to detect and observe its presence. If the condition is progressive early operation is necessary, but one must be quite certain of the diagnosis. For example, mere inability to pass a ureteric catheter does not necessarily indicate a stricture. A rigid orifice which will not admit a catheter may nevertheless allow urine to escape freely and may even permit ureteric reflux. Such reflux may be the original cause of the renal back pressure, and it is obvious that re-implantation of a ureter dilated due to reflux would make matters worse, not better. It is therefore important to perform, not only an excretion pyelogram to ascertain the state of the upper tract and the degree of dilatation of the lower ureter, but also a micturating cystogram to detect reflux, even if a stricture is suspected because a catheter will not pass up the ureter.

On occasion the excretion pyelogram may show a dilated kidney without demonstrating the ureter. If in such a case a ureteric catheter cannot be passed, we do not know whether the obstruction is at the pelvi-ureteric or at the uretero-vesical junction, or both, and although a cystogram may help, the possession of a previous set of radiographs may be quite invaluable as indicating a tendency to narrowing at any given point. A kidney which was previously known to possess a normal pelvi-ureteric junction, but which suddenly ceases to concentrate opaque medium owing to a stricture of the lower ureter, is always worth trying to save by excising the stricture. Some function will nearly always return to the kidney.

Ureteric re-implantation to the bladder

We have not experienced any success from attempts at per-urethral dilatation of ureteric strictures, nor have we found it practicable to form valvular orifices at the site of re-implantation owing to the thickening of the ureter, and we are now content with a simple mucosa-to-mucosa anastomosis.

swabs. The cavity walls must be cleaned in this way until healthy granulation tissue is reached, but great care must be taken to avoid too vigorous swabbing which will cause troublesome oozing. When the cavity has been cleaned, the remainder of the roof should be excised carefully with scissors taking great care to ensure that a very definite overhanging edge remains all round the cavity (Fig. 55). Any areas of oozing can be controlled by oversewing with fine catgut on an atraumatic needle (Fig. 56). If the overhanging edge has been removed the sutures cut out and even tend to increase the bleeding, so that any attempt to saucerize the cavity must be avoided—as must any desire to probe the closed-off neck of the calyx. With due care there should be no difficulty in achieving complete haemostasis. The operation is now virtually over. The kidney is allowed to drop back into its bed, and the wound is closed without any drainage whatever. No tubes or irrigations of any sort are used.

We have performed over 30 cavernotomy operations without mortality or morbidity. No urinary fistula has developed but one skin sinus has been excised. Several multiple and bilateral operations have been performed, the maximum amount of pus evacuated being 180 millilitres from five cavities in the two kidneys of one patient.

It should not require emphasis that surgery cannot replace or shorten prolonged drug therapy, either before or after operation.

THE PELVI-URETERIC JUNCTION

Obstruction at the pelvi-ureteric junction, be it due to active disease or healing fibrosis, is the most serious lesion encountered in renal tuberculosis, since it produces a simple, old-fashioned pyonephrosis, and this is now the only remaining indication for nephrectomy.

When first confronted with a strictured junction and a pyonephrosis, there should be no indecent haste to resort to surgery because even the most advanced radiological appearances can change dramatically after three months' intensive drug therapy. Grossly "blown" calyces in themselves are no indication for nephrectomy provided the pelvi-ureteric junction is clearly defined and patent. Such a kidney may "heal" though it will always show radiological distortion. However, when the junction is seriously involved from the outset a nephrectomy will usually be necessary eventually.

It will occasionally happen that during the course of drug treatment, the healing fibrosis at the junction produces progressive narrowing, and in three such cases we have performed a successful plastic operation using the Davis intubated ureterostomy technique. All three patients now have sterile urines and functioning kidneys.

The difficulty with this type of surgery is to decide when to operate. It must obviously be before the obstructive process has destroyed too much renal tissue, and in spite of the good results we feel that we should have operated upon our own cases earlier than we did.

LOWER URETERIC OBSTRUCTION

The lower segment of the ureter is normally empty and it is very unusual to see it outlined with opaque medium during excretion pyelography except perhaps in one

film of the series. This is because urine passes through this segment very rapidly and is not normally held up at the uretero-vesical junction. However, minor degrees of bladder or urethral irritation can cause oedema or spasm in this region so that both lower ureters may remain filled (not necessarily dilated) throughout the whole period of a pyelogram investigation. This is a non-specific reaction and is frequently seen in cases of cysto-urethritis, especially in young women. It is transitory and disappears completely when the cysto-urethritis subsides. Such a radiological picture may be one of the earliest signs of renal tuberculosis, particularly in patients whose presenting symptoms are due to bladder and urethral irritation, and is again a non-specific reaction.

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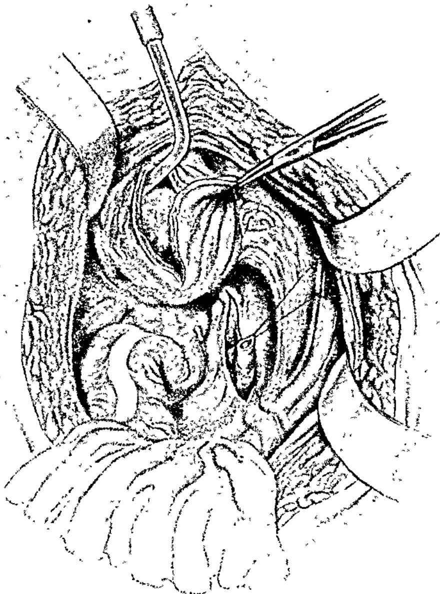


FIG. 57.—Ureteric re-implantation. Dilated ureter isolated above strictured area adjacent to trigone. Boari flap fashioned from bladder vault.

A majority of tuberculous strictures are situated within a few centimetres of the uretero-vesical orifice (without exception in our series) so that only very rarely is it impossible to re-implant the ureter into the bladder, particularly if use is made

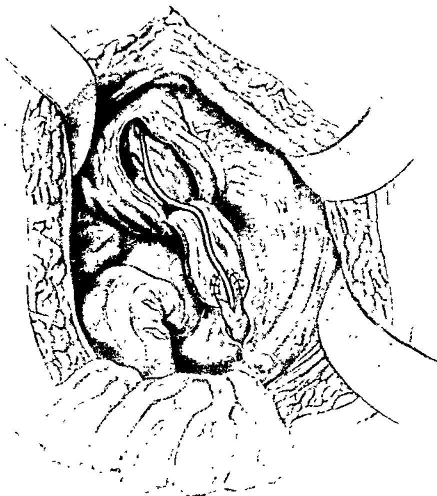


FIG. 58.—Ureteric re-implantation. Ureter attached to open flap. Suturing over a splint considerably simplifies the anastomosis even if the splint is removed at the end of the operation. The bladder is drained by a urethral catheter.

of a Boari flap, which will easily compensate for the loss of about 7 centimetres of ureter (*see* Fig. 59).

Ureteric reflux will nearly always occur to some extent after a simple mucosa-to-mucosa anastomosis, but this is much less dangerous than recurrent stricture

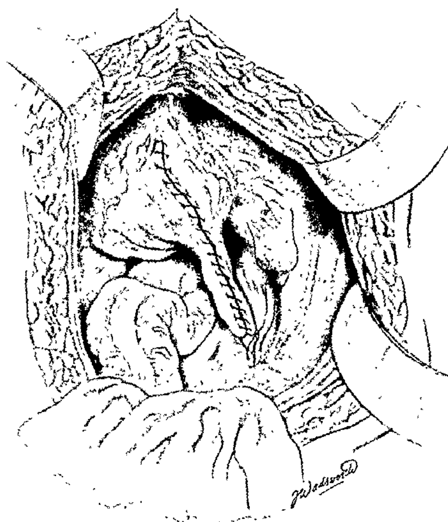


FIG. 59.—Ureteric re-implantation. Completion of the pedicle tube; tight closure of the bladder; a deficiency of approximately 7 centimetres of ureter can be overcome by this means.

formation which followed two of our earlier cases where we attempted to form a valvular junction, and the degree of reflux, particularly after a Boari flap, has not been serious enough to detract from the obvious benefits of a simple anastomosis.

It is clear that any form of re-implantation into a small contracted bladder would be extremely difficult if not impossible, but fortunately the need seldom

arises. A small bladder will require an ileocystoplasty, and only if the ureters are mechanically stenosed will it be necessary to re-implant them into the ileal bladder. Reflux is probably a contra-indication for touching the ureters, since the enlargement of the bladder *per se* considerably reduces the degree of reflux.

Technique

Ureteric re-implantation is not a technically difficult operation. A paramedian incision provides adequate access to the retroperitoneal space, where the ureter can generally be detected by its size and perhaps thickness and rigidity. There is no need to dissect out the stenosed portion of ureter close to the trigone. This can safely be left *in situ* because in all of our early cases the histology of the stenosed stump showed simple chronic inflammatory fibrosis without any evidence of tuberculous disease.

The technique of the Boari operation is shown in Figs. 57, 58, 59. The suturing of the funnel is much simpler if performed over a ureteric splint which can be left *in situ* for 5–6 days if desired, while the bladder can be closed tightly and drained per urethram for 10 days.

THE SYSTOLIC BLADDER

While renal tuberculosis is a silent disease, bladder involvement is certainly not, and a majority of patients present with symptoms referable to the bladder and urethra. Fortunately when diagnosed early a tuberculous cystitis responds well and rapidly to modern drug therapy, and the improvement in frequency and dysuria during the first few months of treatment is sometimes dramatic. Unfortunately if the mucosa is eroded down to the muscle, "healing" may occur by fibrosis, and although the mucosa will re-epithelialize, the muscle will continue to contract down producing a systolic bladder, which is one of the most distressing results of urinary tuberculosis. Quite apart from the misery of frequency, strangury and eventual incontinence, the systolic bladder is dangerous owing to its effect upon renal function. It is generally associated with severe ureteric reflux, and even when the tuberculous focus has been cured, obstructive renal failure is progressive.

In the recent past this condition generally presented as a late manifestation of a healed or quiescent renal tuberculosis which had burnt itself out, or where a kidney had been removed many years previously, leaving a bladder which continued to contract over the years.

In fact the classical picture was of a radiograph showing one absent kidney, a small systolic bladder and a grossly dilated ureter on the "good" side due to continuous ureteric reflux. Most of these patients had a "cured" or quiescent tuberculous infection—otherwise they would have been dead years before. Today the picture has changed. The patient does not die of tuberculosis in the acute phase, both kidneys can probably be preserved, and it is sincerely hoped that the incidence of systolic bladder will be considerably reduced. However, while this is certainly so in the older age groups, many examples are now being encountered in young adolescents who in previous days would have died from their disease before the bladder had time to contract down.

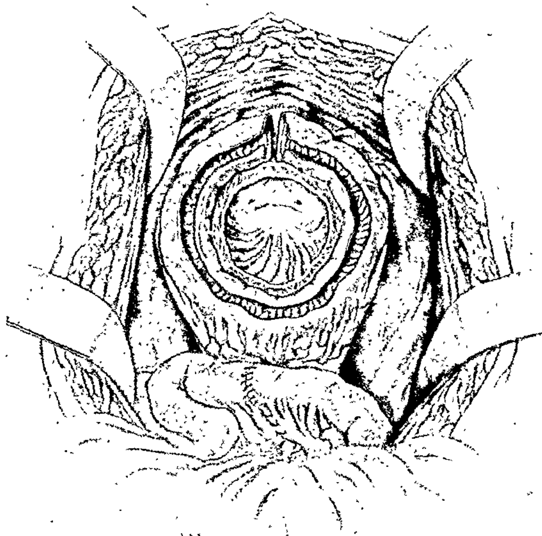


FIG. 60.—Ileocystoplasty (modified after Yeates, 1956). Dome of bladder resected to provide maximum diameter opening. Antimesenteric border of ileal loop fixed to bladder by means of serosal sutures (peritoneum-to-peritoneum where possible). Loop opened up one-eighth inch from attachment (that is one-eighth inch from antimesenteric border).

In the past the standard treatment was urinary diversion to the skin or bowel, but recently most encouraging results have followed the various bladder enlarging operations such as ileocystoplasty or colocystoplasty.

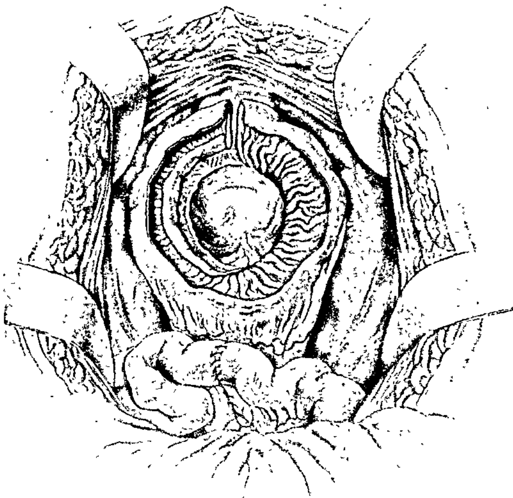


FIG. 61.—Ileocystoplasty. Mucosa-to-mucosa attachment of ileal loops to bladder.

Ileocystoplasty

The various "ring" loop, "T" loop, and "cat's tail" procedures have now given way to the open flap type of operation which empties better than a closed loop and causes much less trouble with mucus (Hanley, 1959). It is important that the

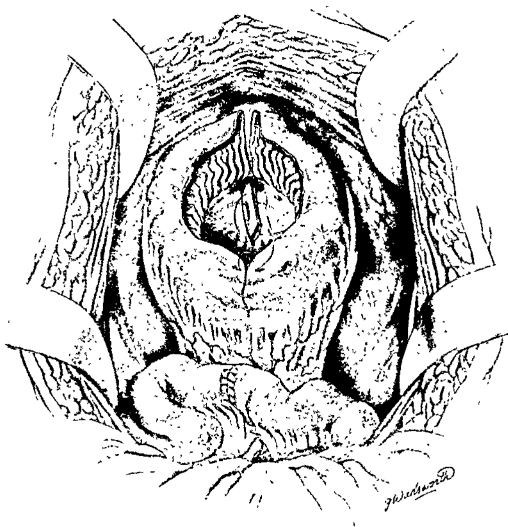


FIG. 62.—Ileocystoplasty. Two-layer closure of new vault of bladder. An eight-inch length of ileum will generally be found to be more than enough, and any redundant material should be resected.

reconstructed bladder should not be too large or voiding will be interfered with, and an open flap made from a six-inch loop of ileum is ideal. On no account must a loop ever be joined to a simple incision in the bladder because contraction of the

stoma will occur. On the other hand, in tuberculous cases there is no need to remove the bladder right down to the trigone (which is usually necessary in cases of severe Hunner's ulceration). In practice we resect the dome of the bladder until an opening of maximum diameter is available for the anastomosis. It is absolutely essential to remove even a minor degree of bladder neck obstruction at the same time.

An open flap operation is illustrated in Figs. 60, 61, 62.

URINARY DIVERSION

Nephrostomy

This operation can be a life-saving procedure and should be performed early rather than later when serious urinary obstruction to the pelvis or ureter is encountered. However, it should be regarded as a temporary measure until renal function is restored and some more permanent and aesthetic procedure can be performed.

Cutaneous ureterostomy

This is easy to perform and carries a low operative mortality, but it is now rarely used by urologists. No one has devised a completely reliable apparatus for collecting urine from the abdominal wall, while the large number of "nipple" operations devised to fit a cup or prevent stricture formation merely indicate that the perfect operation has yet to be invented.

Uretero-colic anastomosis

This procedure is now condemned in cases of tuberculosis because the ureter is always thick walled and dilated, and it is practically impossible to prevent reflux or stricture formation at the stoma or both. Any type of diversionary operation, however successful, must have overwhelming relative advantages to make it more acceptable to a patient than the use of his own urethral sphincter, and it is now generally possible to excise ureteric strictures and enlarge the bladder so that life again becomes acceptable.

CONCLUSIONS

In conclusion one can state that urinary tuberculosis can now be controlled by the prolonged use of suitable drugs. If the urine is not sterilized within two or three months, there is some error in the management of the case, or healing fibrosis is creating closed avascular areas which are not accessible to the blood borne drugs. These may have to be dealt with by surgery.

The majority of complications that occur are due to healing fibrosis which causes urinary obstruction, and this must be relieved by early surgery. Such conservative surgery calls for much more skill, imagination and clinical acumen than does a simple nephrectomy.

For the future, newer and better drugs will doubtless be forthcoming, but apart from being more effective against the tubercle bacillus, they must be less, not more, toxic to the patient than those in present usage before they will become generally acceptable.

REFERENCES

Hanley, H. G. (1959). "Ileocystoplasty (a Clinical Review). *J. Urol.*, **82**, 317.
— (1960). "Conservative Surgery in Renal Tuberculosis." *Brit. J. Surg.* In the press.
Yeates, W. K. (1956). "Discussion. Use of the Ileum in Urology." *Brit. J. Urol.*, **28**, 410.

SELECTED ABSTRACTS

Partial nephrectomy

A critical study

Gow, Ross and Hill (1959) reported on the use of partial nephrectomy in the management of renal tuberculosis. The series of patients comprised 9 women and 28 men. Histopathological examination of the resected renal tissue showed that 6 lesions were active and 4 lesions were moderately active. In 27 cases the disease was quiescent. After the operation 26 patients remained well, with a sterile urine, for 2–6 years. Ten patients appeared to be well, although the urine contained tubercle bacilli. Few signs of improvement were observed on pyelographic examination. The investigators believe that the presence of a sterile urine is of more significance than the radiological appearance. A sanatorium regimen, chemotherapy and elective surgery constitute inseparable components of treatment. Partial nephrectomy is advocated when a cavity continues to secrete tubercle bacilli despite the prolonged use of chemotherapy. Inadequate excision may be responsible for persistent excretion of organisms in the urine. If the upper or lower pole of a duplex kidney and its ureter is diseased the affected portion should be excised. With regard to the surgical technique meticulous haemostasis is essential. If it is not possible to perform a satisfactory V-shaped excision and closure is difficult, grafts of fat or muscle should be placed in the defect. The guillotine type of amputation is not a safe procedure. Operation is not necessarily indicated in the treatment of a sealed-off calyx or a large renal lesion. Furthermore, operation is contra-indicated in patients with a single kidney.

Observations on 211 cases

Puigvert (1959) presented his observations on 211 cases of partial nephrectomy in 209 patients. Although partial nephrectomy is most commonly indicated for renal calculus, it has recently been employed for localized tuberculous lesions. Tuberculous kidneys respond successfully to rigorous and controlled medical treatment, so that nephrectomy is rarely necessary except in cases of pyonephrosis or completely closed non-functioning kidneys. On the other hand, a small localized lesion which becomes separated from the main collecting system even if clinically silent is not a cure. These lesions have great influence on the remainder of the urinary apparatus, and their removal is often sufficient to improve the bladder or ureteric complications. When, in spite of prolonged drug treatment, a localized bacterial lesion persists its removal is justified to preserve the rest of the kidney. Delay in excision of the focus may favour spread of the disease, so that surgery must not be left until it is too late. Sixty-two cases of renal tuberculosis, eight involving a single kidney, were subjected to partial nephrectomy with clinically and radiologically very encouraging results. Among renal malformations, the horse-shoe kidney may require segmental excision which may be considered technically as a partial nephrectomy. In a horse-shoe or L-shaped kidney with a localized tumour, the mass is removed as far as the healthy renal tissues, keeping the maximum amount of parenchyma intact. The same procedure applies to encapsulated tumours, especially within the pole of a morphologically normal kidney, but is only justified when the lesion is localized and diagnosed early. Survival rates of 11 years have been obtained. In large serous cysts and in some cases of multiple cysts, partial nephrectomy is more satisfactory than removal of the cyst. In general the ilio-lumbar incision is adequate; in horse-shoe kidney, however, the transverse incision of Bazy is used. Preventive haemostasis by ligature of the vessels independent of the pre-renal branching of the pedicle is important. By avoiding intra-

cavitary and canalicular drainage both the operative procedures and the functional results are improved. Suture of the edges of the calyx is unnecessary, occlusion depending upon the perfect permeability of the urinary channels. The application of absorbable haemostatic material must be avoided; a piece of dorsal muscle applied to the renal stump should be substituted. The kidney site is drained for 5-6 days; in tuberculous cases, 8-10 days. In 211 operations there were 9 post-operative deaths. In 2 cases second nephrectomies were necessary.

"Cup-patch" technique of ileocystoplasty

Bladder enlargement or partial substitution

GOODWIN, WINTER and BARKER (1959) described the technique of "cup-patch" ileocystoplasty for enlarging the urinary bladder or for partial substitution. The lower part of the abdomen is incised through the midline, appendicectomy is performed and a suitable segment of the terminal ileum is isolated, care being taken to preserve the blood supply. The segment should be 20-25 centimetres in length. Continuity of the ileum is re-established by means of ileo-ileostomy. The isolated ileal segment is irrigated with warm saline solution and opened along its antimesenteric border. The segment is arranged in a U-shaped fashion, the margins are united with continuous interlocking catgut and a cap is constructed for anastomosis to the dome of the bladder. Sometimes it is necessary to excise the dome of the diseased bladder and redundant portions of the ileum. Catheters are inserted in order to identify the position of the ureteral orifices. Encroachment upon the ureteral orifices in the trigone may lead to the development of vesico-ureteral reflux. Sutures are inserted in the posterior part of the bladder and continued laterally. The anastomosis is completed on the antero-inferior surface of the bladder. Urethral and suprapubic catheters are placed in position and drainage is maintained for at least two weeks. The authors carried out the operation in four cases of contracted bladder, and excellent results were achieved. On the other hand, unsatisfactory results were obtained in three of four cases in which the operation was employed in the treatment of neurological disease of the bladder.

REFERENCES

Goodwin, W. E., Winter, C. C., and Barker, W. F. (1959). *Surg. Gynec. Obstet.*, **108**, 240.
Gow, J. G., Ross, J. C., and Hill, C. A. St. (1959). *Lancet*, **2**, 759.
Puigvert, A. (1959). *Mém. Acad. Chir.*, **85**, 177.

RECENT ADVANCES IN BONE MARROW TRANSPLANTATION

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The present great interest in bone marrow transfusion and transplantation in human beings follows directly on a long series of animal experiments beginning with those of Jacobson (1951) and leading to that of Barnes and his colleagues (1956). The bare possibility that this technique could be applied to the treatment of leukaemia in the human stimulated workers in many countries to explore this field. The parallel existence of animal experiments was of the utmost value in that various difficulties and dangers associated with radiation dosage, cell numbers for transfusion, and, in particular, the menace of homologous disease (secondary disease) were known to those desirous of working on these problems. In 1956, the Westminster Group (Humble, 1956) gave moderately large doses of marrow cells ($1{\cdot}019 \times 10^9$ in one case and $0{\cdot}575 \times 10^9$ in the second) to two patients without adverse incident. The first unequivocal evidence of survival of donated bone marrow in the human was reported in 1957 (Thomas and his colleagues, 1957). At the present time it may fairly be said that many of the problems posed by the transition from mouse to man have been overcome. In addition, a further extension of bone marrow transplantation has been employed in that it has been shown possible to remove and store a patient's marrow before undertaking therapy and to reinfuse it at a later date (autologous transplant).

THE PREPARATION AND MANIPULATION OF HAEMOPOIETIC CELLS FOR TRANSFUSION

Haemopoietic cell suspensions for transfusion

Haemopoietic cells for this purpose may be obtained from the human foetus or from the adult. In the latter case, excised ribs, bone marrow removed from donors by aspiration and cadaver marrow from the recently dead have been employed. The suspension thus obtained may be stored for long periods in a medium containing serum and 15 per cent glycerol (Ferrebee and his colleagues, 1959).

Foetal cell suspensions

Foetal cell suspensions (Kay and Constantoulakis, 1959a) are prepared from recently obtained foetuses between 20–28 weeks of gestation. By sterile dissection the liver and spleen are removed, minced with scissors and passed through sterile stainless steel mesh screens of suitable pore size. The suspensions contain about $1\text{–}3 \times 10^9$ nucleated haemopoietic cells. It should be noted that in animals splenic cell suspensions have on occasion caused death unless they had been well washed before infusion (Ferrebee and Thomas, 1958).

Adult cells obtained from freshly excised ribs

The rib is cut into 0·5 centimetre fragments and shaken in a flask containing culture fluid. After sieving and centrifuging the fat is removed, and about $1\text{–}3 \times 10^9$ cells may be obtained (Schwartz and Tocantins, 1959; Pegg and Trotman, 1959; Newton and his colleagues, 1959).

Adult cells removed from recent cadavers

This method has been used in the United States of America. Bodies up to three hours after death are suitable. By sterile dissection the bodies of the vertebrae are exposed and largely removed. Up to 60×10^9 cells may be obtained (Ferrebee and his colleagues, 1959).

Adult cells from donors by aspiration

Compatible donors are given a general anaesthetic for this purpose as prolonged and repeated aspirations of bone marrow are too painful under local anaesthesia. In general, one may use either of two techniques. In the first up to 50 punctures are made in the sternum, pelvis, acromion processes and the spines of the vertebrae. Five millilitres of fluid are removed by forceful suction into syringes moistened with heparin and the contents immediately injected into the recipients (Mathé, 1959a). In the second method the marrow-blood mixture is aspirated into syringes containing heparinized culture medium, the suspension is sieved and centrifuged as previously described. The cell suspensions appear adequate for repopulation of the marrow spaces after 2–4 hours at room temperature and up to 24–48 hours at 4°C. Stored at −79°C. in 15 per cent glycerol they remain active for several months. After rapid thawing the material is well tolerated by the patient despite the large amounts of glycerol that are infused.

CLINICAL APPLICATIONS

Bone marrow transplants have been employed in the treatment of human disease under the following conditions.

(1) Attempts to treat leukaemia using high dosage radiotherapy followed by autologous, isologous (twin), or homologous (donor) marrow.

(2) Treatment of aplastic anaemia due to irradiation.

(3) Treatment of aplastic anaemia due to other causes.

(4) Treatment of extensive malignant disease by high dosage large volume radiotherapy followed by an autologous transplant.

(5) Treatment of extensive malignant disease by high dosage chemotherapy followed by an autologous transplant.

(6) Whole body radiotherapy followed by donor marrow as an aid to organ grafting.

Whole body irradiation in the human

Irradiation of the entire body, even that of a child, poses special problems for the radiotherapist. Ideally there should be a pair of opposed radiation sources so that the patient may be placed in a zone of homogeneous irradiation (Thomas, Lochte and Ferrebee, 1959; Mathé and his colleagues, 1959a). Such facilities are rarely available in most radiotherapy departments and a compromise has to be made. Using a two megavolt Van de Graafe generator it is possible, by increasing the target skin distance from one metre to three metres, to subtend an area covering the whole of the child. Even so, the child has to be treated in a cramped position, either sitting up or lying on the side with head and legs flexed. A dose rate at the skin surface of approximately 3 roentgen (r) per minute is obtained. This is twice the dose rate which was used by Mathé and his colleagues, who gave a total dose of 850–900r divided into two daily treatments. It should be emphasized that little is known concerning this type of treatment in the lethal dose range for man. The questions of fractionation of the treatment and the total dose to be attempted are still to be determined.

The treatment of leukaemia

It must be stressed that up to the present date no author has claimed to eradicate leukaemia in the human by this technique even with doses of about 1,000r. However, it is possible to produce a remission of the disease process; the length of this is conditioned by the tissue dose employed, and with total doses in the 1,000r range remissions for long periods up to six months have been obtained. Small dosage (up to 400r) produces short remissions, larger doses (400–600r) are not sufficient to permit a take of donor marrow, still larger doses if donor (homologous) marrow be used invoke the danger of "homologous disease" in the recipient (Mathé, 1959a, b). Experience has shown that this therapy cannot be employed in the terminal case. Any patient so treated must be nursed in strict isolation as infection is rapid and fulminating due to loss of "immunity" and of leucocytes. It is a well known feature of acute leukaemia in children that apparently complete remissions may be obtained by "antimetabolic" drugs such as 6-mercaptopurine and amethopterin and also by the corticosteroid hormones. In these remissions the bone marrow may appear quite healthy. This marrow has therefore been taken and stored so that when the patient relapses he may be treated by irradiation followed by reinfusion of his own marrow (autologous transfusion).

This manoeuvre has been attempted in three cases (McGovern and his colleagues, 1959). In one only was a very prolonged remission obtained. In the special instance of leukaemia occurring in one of a pair of identical uniovular twins the healthy twin may be used as a donor (isologous transfusion). The restoration of marrow function is extremely rapid. The procedure appears to have been attempted four times and varying lengths of remission were obtained. One such case is reported by Atkinson and his colleagues (1959).

Leukaemia treated by radiotherapy followed by donor (homologous) marrow

There are records in the literature of some 40 cases so treated. Of these about 15 went into remission for a short or long time. Long remissions are usually obtained only by dosage in the region of the so-called lethal dose (Mathé and his colleagues, 1959a; Ferrebee, 1959). It should be noted that Mathé and Bernard (1959) reported that of six children so treated four developed secondary disease some 40 days after the irradiation and two apparently died of it. There is some evidence that this complication may be amenable to treatment with corticosteroids. Further experiments are now actively being carried out with more fractionated exposure to the irradiation, and especially directed to the recognition and treatment of secondary disease.

Aplastic anaemia following accidental irradiation

Homologous transplants of fresh donor marrow were used to treat five out of six Yugoslav physicists who were accidently irradiated in a reactor accident (Mathé and his colleagues, 1959b; Jammet and his colleagues, 1959). The victims had received doses of about 1,000r whole body irradiation. Fifteen days after the exposure they presented a picture of complete marrow aplasia. The most heavily irradiated case died but the other four made a complete recovery. It was demonstrated by blood group antigenic differences that a take of the donor marrow occurred in these patients. Their grafts remained active for about a month then disappeared as the patient's own marrow cells fully recovered their function. The marrow transplants were undoubtedly life-saving in these cases.

Aplastic anaemia not caused by irradiation

Some authors have claimed successes in the treatment of aplastic anaemia not caused by irradiation with large doses of cells (homologous transplants). (Damashek, quoted by McFarland, 1958; Kay and Constantoulakis, 1959b). Both adult and foetal cells have been employed but the overall results cannot be described as encouraging. However, cessation of haemorrhage for a short or longer period has been noted in several instances. Taken as a group these cases do not show evidence of impaired "immunity" and the transplants do not take. Splenectomy followed by marrow infusion would seem worthy of a trial in suitable cases.

Treatment of extensive malignant disease by high dosage large volume radiotherapy followed by autologous marrow reinfusion

One of the limiting factors of irradiation to large volumes of the body is the severe haemopoietic and lymphopoietic depression which commonly follows such treatment. It is well known that red marrow irradiated to more than 2,000r will be seriously damaged and may remain permanently hypoplastic. In an endeavour to prevent this, bone marrow has been taken from the patients before treatment, stored at −79°C. and reinfused after completion of the treatment period (Kurnick and his colleagues, 1959; Newton and his colleagues, 1959). In five out of seven cases known to the authors the injected marrow cells recolonized the aplastic

sternum very rapidly. This was accompanied by haematological improvement in the patients treated.

Treatment of disseminated malignant disease by massive chemotherapy followed by autologous marrow reinfusion

In this case, the previous storage of the patient's marrow has permitted treatment of the disease process with doses of drug (for example, nitrogen mustard, mannitol mustard, and so forth) certain to cause aplasia of the marrow (McFarland, Granville and Damashek, 1959; Westbury and his colleagues, 1959). The authors have noted three complete recoveries of marrow function out of eight cases treated. Death occurred in the other five before marrow recovery could begin.

Whole-body irradiation, donor marrow infusion and organ grafting

Main and Prehn (1955) showed that skin grafts will take in mice if the recipient receives whole body irradiation followed by bone marrow from the presumptive donor. This has also been demonstrated in the human being (Thomas, Lochte and Ferrebee, 1959).

Following these experiments and others carried out successfully in beagles (Ferrebee, 1959), the operation of kidney grafting (renal homograft) has been attempted in at least six cases. Two cases, each in non-identical twins, have been successful. In a third, father to daughter, the graft functioned for 30 days before the recipient died of an intercurrent infection.

FUTURE APPLICATIONS

This review at first sight suggests that the results obtained in the human being are but little reward for so much hard work and such high hopes of success. There are other fields yet untouched. Mice of a certain strain carry an anaemia genetically determined which closely resembles Mediterranean anaemia (thalassaemia) of the human. It was found that the severely affected mice, following whole-body irradiation, would retain a marrow graft from normal members of this breed very well indeed. They were found to maintain normal blood values for an extremely long period of time (Russell, Smith and Lowse, 1956). It is not beyond the bounds of possibility that these results could be applied to the severe homozygous states which are seen in the human in Mediterranean anaemia (thalassaemia major), sickle-cell anaemia and haemoglobin E disease. Even the results in leukaemia are noteworthy, when one remembers that the remissions obtained have been often prolonged in patients in whom conventional therapy had nothing further to offer. The use and possibilities of stored autologous marrow in the chemotherapy of disseminated malignant disease are again a rich field for future experimental work. It is certain that these studies have shown a new light on bone marrow growth and function in the human being and have thus greatly extended our still limited knowledge of this unique body tissue.

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REFERENCES

Atkinson, J. B., Mahoney, F. J., Schwartz, I. R., and Hesch, J. A. (1959). *Blood*, **14**, 228.
Barnes, D. W. H., Corp, M. J., Loutit, J. F., and Neal, F. E. (1956). *Brit. med. J.*, **2**, 626.
Damashek, W. (1958). Quoted by McFarland. *Blood*, **13**, 1096.
Ferrebee, J. W. (1959). Personal communication.
— and Thomas, E. (1958). *Ann. intern. Med.*, 49, 987.
— Atkins, L., Lochte, H. L. Jnr., McFarland, R. B., Jones, A. R., Dammin, G. J., and Thomas, E. (1959). *Blood*, **14**, 140.
Humble, J. G. (1956). *34th Annual Report of the British Empire Cancer Campaign*, p. 184.
Jacobson, L.O., Simmons, E.L., Marks, E.K., Gaston, E.O., Robson, M.J., and Eldredge, J.H. (1951). *J. Lab. clin. Med.*, 38, 330.
Jammet, H., Mathé, G., Pendic, B., Duplan, J.-P., Maupin, B., Latarjet, R., Kalic, D., Schwarzenberg, L., Djukic, Z., and Vigne, J. (1959). *Rev. franç. Ét. clin. biol.*, **4**, 210.
Kay, H. E. M., and Constantoulakis, M. (1959a). *Brit. med. J.*, **1**, 575.
— — (1959b). A paper read at the Seventh European Congress of Haematology.
Kurnick, N. B., Montano, A., Gerdes, J. C., and Feder, B. (1958). *Ann. intern. Med.*, **49**, 973.
Main, J.M., and Prehn, R.T. (1955). *J. nat. Cancer Inst.*, **15**, 1023.
Mathé, G. (1959a). *Congr. Coll. Univ. Liege*, **12**, 314.
— (1959b). 1er Symposium international de Chimiothérapie anti-infectieuse et antimitotique. 12 et 13 Septembre.
— and Bernard, J. (1959). A paper read on 9th September at the Seventh European Congress of Haematology.
— — Schwarzenberg, L., Larrieu, M.-J., Lalanne, Cl-M., Dutreix, A., Denoix, P. F., Surmont, J., Schwarzmann, V., and Céora, B. (1959). *Rev. franç. Et. clin. biol.* **4**, 675.
— Jammet, H., Pendic, B., Schwarzenberg, L., Duplan, J.-F., Maupin, B., Latarjet, R., Larrieur, M. J., Kalic, D., and Djukic, Z. (1959b). *Ibid.*, **4**, 226.
McFarland, W. (1958). *Blood*, 13, 1096.
— Granville, N. B., and Damashek, W. (1959). *Ibid.*, **14**, 503.
McGovern, J. J., Russell, P. S., Atkins, L., and Webster, E. W. (1959). *New Engl. J. Med.*, **260**, 675.
Newton, K. A., Humble, J. G., Wilson, C. W., Pegg, D. E., and Skinner, M. E. G. (1959). *brit. med. J.*, **1**, 531.
Pegg, D. E., and Trotman, R. E. (1959). *Brit. J. clin. Path.*, **12**, 444
Russell, E. S., Smith, L. J., and Lowse, F. A. (1956). *Science*, **124**,. 1076.
Schwartz, R., and Tocantins, L. M. (1959). *Blood*, **14**, 91.
Thomas, E. D., Lochte, H. L., Jnr., and Ferrebee, J. W. (1959). *Blood*, **14**, 1.
— — Lu, W. C., and Ferrebee, J. W. (1957). *New Engl. J. Med.*, **257**, 491.
Westbury, G., Humble, J. G., Newton, K. A., Skinner, M. E. G., and Pegg, D. E. (1959). *Lancet*, **1**, 968.

SELECTED ABSTRACTS

Whole-body irradiation and marrow transplantation

In this communication THOMAS, LOCHTE and FERREBEE (1959) discussed further clinical experiences with whole-body irradiation and marrow transplantation in man. They describe 12 cases fully and discuss their physical and biological problems. Exposure to ionizing radiation is followed by impaired cell division. After whole-body irradiation (300 –700 roentgens) death is due to marrow failure. As the primitive cells cannot divide there is no production of platelets, leucocytes and erythrocytes. The loss of leucocytes and a lower concentration of defence elements, immune globulin and properdin produce

a prostrate host in whom infection flourishes. In this prostrate host the liberal growth of homografts of normal marrow indicated a means of healing the post-radiation syndrome. The host can, by irradiation, followed by marrow transplantation, restore his lymphoid defence system. He will produce and tolerate cells of the blood type of the donor up to a certain level of acceptance. Too little radiation destruction of the host's defences or too foreign a graft may cause a reaction with subsequent infection and slow death. The well-irradiated host does not react against the graft, and the immature and tolerant graft does not react against the host. Thus infusion of haematopoietic cells of foetal liver is followed by a good recovery of circulating blood elements and no delayed foreign bone marrow reaction. Another cause of immunologic crippling is because marrow is a poor source of cells of the splenic or lymphoid follicle type that are needed for prompt restoration of lymphoid functions. In man these difficulties might be solved by (1) determining whether immunologically mature and reactive cells of lymphoid type are present in adult human marrow in troublesome numbers; (2) their removal from marrow used for infusions or the use of foetal haematopoietic tissue lacking mature reactive lymphoid elements; and (3) the addition to marrow of such tolerant lymphoid elements of immature foetal spleen as may be necessary for the repair of the lymphoid system and its antibody functions. The use of mature spleen or lymph nodes is clearly contra-indicated in homologous transfers. Infection is the chief problem after whole-body irradiation, particularly in the terminal leukaemic patient. Assessment of the control of leukaemia by radiation and marrow transplantation must await facilities for administering radiation in a sophisticated fashion consistent with the patient's own interest. In the treatment of leukaemia total-body irradiation cannot be called the optimal treatment. Its effects on normal and neoplastic tissue are too indiscriminate. Chemotherapy, oncolytic virology or some other specific approach through the emergent immunology of cancer, appeals to the authors.

Transfusion and grafts of homologous bone marrow

Accidental irradiation of human beings

MATHÉ and his colleagues (1959) discussed transfusions and grafts of homologous bone marrow in human beings accidentally irradiated at high doses. Five physicians were accidentally submitted to high doses of neutrons and *gamma*-radiations from a reactor. These dosages were estimated and tended to be confirmed by the haematological disorders observed. Symptomatic treatment, designed to prevent a severe anaemia or haemorrhagic syndrome and to restore the leucocyte deficiency, was instituted. Blood cytopenia was tolerated until the twenty-fifth day after irradiation. In view of the deteriorating condition of one patient, a trial of embryonic marrow cell graft was decided upon. He received, intravenously, 4 milliards 260 millions of free nucleated cells taken from the spleen and from the liver of a 5-months foetus a few hours after premature death. No clinical nor haematological results were observed for a few days. After 11 days, however, an intestinal syndrome developed, with pain in the iliac fossa. It was then decided to give him a transfusion of medullary cells from a voluntary adult donor. This resulted, 4 days later, in a rapid rise in the blood cells. Nevertheless, the intestinal symptoms increased; anuria and signs of acute renal insufficiency ensued. Death occurred from haemorrhage of the respiratory tract. The haematological result in this case and the aggravated signs in the others suggested an intravenous transfusion of marrow cells from adult donors: one donor for one recipient of the same sex. The haematological and clinical states of the four remaining patients thus treated immediately improved. A rapid elevation of the counts of reticulocytes, granulocytes and blood platelets occurred, followed by a rise in red blood cell concentration. A remarkable improvement in the clinical condition was observed as the granulocyte count rose. The temperature fell to normal, appetite was restored and weight gained. The blood group phenotypes were studied by a modified Ashby agglutination method. It was found that the curve, or curves, of the antigens peculiar to each donor, rose to a maximum, then began to fall, about a month after transfusion of the bone marrow. It was further found that during the period of rise the curves were, for every recipient, parallel with the blood concentration curves. The correction of anaemia, therefore, seems intimately bound up with the erythrocyte production of the graft, the phenotypes of the red cells

being produced respectively by the grafted marrow and the patient's own haemopoietic tissue.

Leukaemia

Treatment by total irradiation and transfusion of homologous bone marrow

MATHÉ and his associates (1959) described a trial of treatment by total irradiation followed by transfusion of homologous bone marrow in three children with acute leukaemia in remission. The history of their illnesses up to the time of irradiation is recorded. The technique of the irradiation by cobalt 60 with a dosage of 850 rads is described. With one exception, the patients received phenothiazine and chlorpromazine beforehand. The graft was taken from voluntary donors with blood group phenotypes corresponding to the respective recipients and was injected intravenously without being filtered. After irradiation the patients were isolated. Antiseptic treatment was instituted and they were given oral sulphonamides and streptomycin to reduce intestinal flora; *gamma* globulins were also given. When fever appeared blood cultures were made; these were consistently negative. Haematological and haemostatic studies were undertaken; fluid and electrolyte disorders were corrected; alimentation was provided by amino acids, glucose, sorbitol and vitamins. The clinical course of each case and the results of treatment are described in detail. Digestive disturbances and a lymphoid and myeloid pancytopenia were early occurrences. Irradiation itself produced nausea and vomiting, particularly during and at the end of the first fraction. The intensity of the symptoms led to electrolyte investigation, disclosing a tendency to hypochloraemia and a notable hypokalaemia. Cutaneous symptoms appeared during the fortnight after irradiation and included a fine desquamation all over the body. The hair began to fall towards the tenth day, with complete alopecia towards the thirteenth day. A period of total aplasia followed. The lymphocyte count was notably diminished the day after the first fraction of irradiation and "broken down" the day after the second. The reticulocytes had practically disappeared between the fourth and fifth days; granulocytes between the fourth and sixth. Platelets fell more slowly; anaemia only became significant 12 days after irradiation. The toleration of cytopenia was good for about six days in all patients, but diminished between the eighteenth and twenty-eighth days and was followed by fever, stomatitis, necrosis and a haemorrhagic tendency. One child died from respiratory complications before any evidence of marrow activity occurred. In the two surviving children, clinical symptoms disappeared from the time of reappearance of the circulating granulocytes. The study of the phenotypes showed the presence, after three months, of red cells bearing the antigenic characteristics of the donors, the curve indicating the production of erythrocytes by the patients' own marrow. The most striking clinical observation was secondary disease of acute onset, having the same characteristics in both cases and appearing about the forty-fifth day after irradiation and 15 days after medullary restoration. It ended about six months after irradiation, coinciding with a rise in the lymphocyte count and the simultaneous disappearance of the red cells of the donor phenotype, which had remained level for the previous three months. The manifestations were digestive disturbances, loss of weight, abnormal *gamma* globulins and lymphoid aplasia. The significance of the disease is difficult to determine. A relapse of the leukaemia occurred after six and five months of complete remission.

Treatment of terminal relapse

MCGOVERN and his colleagues (1959) pointed out that in children with acute leukaemia the bone marrow may become normal for a time during a remission induced by one of the chemotherapeutic agents. Thus, in some cases the marrow may provide autologous material for subsequent use as a marrow autograft. The infusion of autologous marrow in animals and isologous marrow in man, after potentially lethal doses of radiation or chemotherapeutic agents, can protect against their lethal effects by restoring the marrow-cell population. Marrow can be stored in glycerol at −70°C., and still remain viable for its eventual use as an inoculum for the repopulation of the affected marrow spaces. An investigation was reported on three patients on the effects of preserved autologous marrow,

taken during a period of remission from leukaemia, and later infused after the patient had received a potentially lethal dose of total-body radiation in a period of critical relapse. The bone marrow was obtained by multiple, bilateral aspirations of iliac bone, under anaesthesia, within an hour after the patient was irradiated. The concentrated marrow cells were infused. Careful neutralization of heparin was also found to be important. Case 1 survived for nine days after irradiation; leukaemia was found at necropsy. Case 2 showed within 17 days a restoration of normal bone marrow and of peripheral blood. This was possibly due to the effect of the transfused autologous marrow. It is possible also that this good effect was due to spontaneous recovery after whole-body irradiation of 570 roentgen during a critical relapse of leukaemia. Against this, however, is the fact that in case 2 the formed elements of the blood reappeared at a different time and in a different sequence. For instance, in cases which recovered spontaneously the reticulocytes and platelets reappeared in the peripheral blood before the leukocytes. In case 2 the leukocytes were the first to reappear in the peripheral blood and as early as ten days after irradiation. The child was alive, well and happy three months after the irradiation. The peripheral blood picture was then normal.

Treatment of malignant disease

Autologous bone marrow infusion

Autologous bone marrow infusion as an adjunct in the therapy of malignant disease is discussed by McFarland, Granville and Dameshek (1959). In cases of lymphosarcoma and Hodgkin's disease remissions can usually be obtained by radiotherapy or alkylating agents early in the disease. But in relapse or in long-standing cases, more vigorous therapy is often impossible because of the depressant effect on the bone marrow. After massive radiotherapy or chemotherapy, efforts to revive the marrow cells by homologous bone marrow transplantation are usually unsuccessful, probably because of an immune reaction between host and transplant. The use of the patient's own (autologous) bone marrow prevents this reaction and should permit larger dosage of x-ray with survival of bone marrow. Five advanced cases, two with lymphosarcoma and three with Hodgkin's disease, were given massive intravenous doses of nitrogen mustard to destroy all neoplastic tissue. (The large dosage did not provoke any more nausea than the usual dosage.) This was followed by the intravenous injection of autologous bone marrow to aid the recovery of the patient's bone marrow. Two of the five patients died of infection. In one patient the gastro-intestinal mucosa was severely macerated at necropsy, suggesting that in the range of 1·1–1·4 milligrams per kilogram nitrogen mustard severe gastro-intestinal damage may follow on bone marrow destruction. In three patients the tumours, fevers and sweats disappeared for two months before symptoms recurred. The fewer tumour cells present per dose of chemotherapeutic agent the greater the chance of cure. It may be that if these massive doses were used early in the disease when few malignant cells were present, there may be more prolonged remissions or even cure. The administration of chemotherapeutic agents prophylactically, following surgical excision of a primary malignancy, is being widely investigated. If these results are not favourable with standard doses, it is possible that larger amounts followed by autologous bone marrow transfusion might be suitable. In the surviving patients in the present series there was return of the marrow and peripheral blood elements essentially to normal values within one month. Whether this period was shorter than would have occurred without giving autologous marrow can only be surmised. The method, in any case, warrants further study.

Viable cadaver bone marrow

Collection, storage and preparation for intravenous use

Ferrebee and his colleagues (1959) pointed out that the intravenous administration of viable marrow cells to animals brings about a repopulation of marrow spaces rendered aplastic by radiation, chemotherapy or natural processes. Cells from suitable donors, isologous, homologous or heterologous may be used fresh or after storage in glycerol at −80°C. This has led to a study of the methods for the collection and storage of human

marrow. One or two billion (one American billion = 10^9) nucleated cells may be obtained from a foetus or from aspiration biopsy of the ilium. As the adult cadaver appears to be the largest potential source of cells, the problem of collecting and storing cadaver marrow for intravenous use has been considered. Adult cadavers dying of blood loss, coronary disease or other non-septic conditions are suitable, provided no more than four hours have elapsed since death. Under sterile conditions the vertebral column from the upper thoracic portion to the fifth lumbar vertebra is exposed and the anterior portion of the column is excised. The exposed marrow is then removed from the vertebral bodies, avoiding the intervertebral discs. The marrow must now be freed from tissue and other foreign material to prevent the occurrence of pulmonary emboli after intravenous injection. It is passed through a number of stainless steel screens. The marrow particles are thus in a suspension of single cells without being damaged. The marrow is then centrifuged and suspended in an equal volume of 30 per cent glycerol and 70 per cent human serum. It is then frozen to −80°C. and stored. It is prepared for intravenous use by thawing. A half volume of 35 per cent glucose in water is next added, and after two minutes one volume of isotonic saline solution followed after two minutes by a further volume of saline solution. The final suspension contains about 20 billion nucleated marrow cells in 2·5 per cent glycerol and slightly hypertonic glucose-saline solution. The authors have not infused glycerolized cells in man without first reducing the glycerol to 2·5 per cent or less. Human marrow frozen to −80°C. without glycerol loses its ability to synthesize desoxyribonucleic acid. This method of collecting cadaver marrow provides marrow sufficient for most *in vivo* and *in vitro* studies.

Foetal tissue bank

KAY and CONSTANDOULAKIS (1959), in discussing the prospects of a foetal tissue bank, stated that grafts of living cells exchanged between unrelated members of a species are destroyed by an immune response of the host's lymphoreticular system—the homograft reaction. If the graft is "insulated" or if the host's immune mechanism is weak, this reaction does not occur. A high dosage of whole-body irradiation makes bone-marrow replacement essential if the patient is to survive. The development of marrow-assisted recovery is influenced by the dose of radiation, the "compatibility" of the graft, and the number of grafted lymphoid cells. Blood cells in foetal life are derived mainly from the liver; the spleen, because of its lymphopoietic and some myelopoietic activity may be of additional value. A short term culture of a sample of suspended cells from liver and spleen is made and the remainder stored. Short term culture will indicate the activity of the cells; for example, their capacity to synthesize nucleic acid (DNA). There is, as yet, no method for growing useful cells by long-term culture. The standard preserving medium for bone marrow is 15 per cent glycerol in serum, but there is no proof yet that this is the optimum for man. In dealing with the many different cells of the foetal liver their freezing optima are difficult to obtain but the technique of autoradiography shows that DNA synthesis continues after freezing and thawing in 15 per cent glycerol-serum; though the survival of the important and relatively few stem-cells by this technique is not definitely known. Storage of frozen tissue can be by liquid nitrogen, dry ice crushed or dissolved in alcohol, or by mechanical refrigeration. Suspensions of haemopoietic cells can be given intravenously by slow injection. Frozen cells should be quickly thawed and injected immediately. It has been shown experimentally that cells so given find their way to their correct place in the body and there they remain and increase. The antigens of foetal blood cells are well developed, probably from the time they first form. The only exception appears to be the ABO system where, for instance, the A_1 character is never present before birth. Foetal erythrocytes are easily typed, and the authors' routine practice is to determine the ABO, D, C, E, c̄, ē, M, N, S, Fy^a and K groups, since incompatibility of mother and foetus may be the cause of some of these abortions; an excess of certain blood groups might well be expected, particularly ABO antigen differences. However, the authors' figures have revealed, if anything, a slight excess of group O foetuses—the opposite to what might be expected. There is evidence that certain foetal cells, when transplanted, can overcome the normal homograft barrier and that the parathyroids, for instance, may survive and

function in their new host. If this does prove to be so, a new basic form of endocrine therapy, a kind of "spare parts" service may well arise. For research (in human biology) the supply of human foetuses upon which it largely depends are naturally limited. Fresh foetuses usually are from the middle period of pregnancy (12–28 weeks) when foetal death is quickly followed by delivery. Little is known of the growth and development of the human foetus, though studies are being made of the various foetal systems, including the blood and the radioactive substances in foetal bones.

REFERENCES

Ferrebee, J. W., Atkins, L., Lochte, H. L. Jnr., McFarland, R. B., Jones, A. R., Dammin, G. J., Thomas, E. D. (1959). *Blood*, **14**, 140.
Kay, H. E. M., and Constandoulakis, M. (1959). *Brit. med. J.*, **1**, 575.
Mathé, G., Bernard, J., Schwarzenberg, L., Larrieu, M.-J., Lalanne, C. M., Dutreix, A., Denoix, P.-J., Surmount, J., Schwarzmann, V., and Céoara, B. (1959). *Rev. franç. Ét. clin. biol.*, **4**, 675.
— Jammet, N., Pendic, B., Schwarzenberg, L., Duplan, J.-F., Maupin, B., Latarjet, R., Larrieu, M.-J., Kalic, D., and Djukic, Z. (1959). *Ibid.*, **4**, 226.
McFarland, W., Granville, Norma B., and Dameshek, W. (1959). *Blood*, **14**, 503.
McGovern, J. J., Russell, P. S., Atkins, L., and Webster, E. W. (1959). *New Engl. J. Med.*, **206**, 675.
Thomas, E. D., Lochte, H. L., and Ferrebee, J. W. (1959). *Blood*, **14**, 1.

HOMOGRAFTS AND THE COMPLEXITIES OF CHIMAERAS

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Homografting, the transference of living tissues from one person to another, would, if practicable, lead to a revolution in surgical treatment. The technical problems have largely been solved by the surgeon. There remains only the tremendous barrier of immunological specificity—the subject of intense activity in biological research as evidenced by the frequency of sponsored conferences on problems of transplantation (Third Tissue Homotransplantation Conference, 1958; Albert and Lejeune-Ledant, 1959; *La Biologie des Homogreffes*, 1958; Fourth Tissue Homotransplantation Conference, 1960).

IMMUNE RESPONSE

The concept that rejection of homografts is due to the elicitation of an immune response by the host against the graft, now universally accepted, was formerly a matter of much debate. The present agreement stems largely from the elegant research and persuasive logic of Medawar (1945).

One of the chief difficulties to be surmounted was the frequent, in fact usual, absence of demonstrable antibodies in the plasma of animals after rejection of homografts. This is now readily explicable in that some antigens call forth humoral antibodies, exo-antibodies, which may be of various molecular weights (for instance $> 10^5 < 10^7$) and electrophoretic mobility (*alpha*, *beta* or *gamma* globulins) in physico-chemical terms, and manifested in different ways by appropriate immunological tests (precipitation, complement fixation, cytolysis, anaphylaxis and so forth). Other antigens evoke apparently no such exo-antibodies, but nevertheless induce a cellular response which produces the same ultimate result, the specific union with and immobilization of antigen. Presumably these sensitized cells elaborate antibody which is fixed on the cell-surface (Berrian and Brent, 1958) or even within the cell—endo-antibodies.

When the immune response is directed against bacteria and their products or against allergens giving rise to immediate responses—the " hay-fever type " of allergy—interest in the past has been concerned largely with the study of the humoral antibodies, perhaps to the neglect of the part played by cellular responses. Nevertheless, it is now well recognized that the response of delayed supersensitivity to Old Tuberculin (for example, the Mantoux test) is a manifestation of the cellular response, the mobilization of sensitized lymphoid cells to the site of deposit of

antigen. Sensitivity to certain organic chemicals has also been investigated (*see* for example, Landsteiner and Chase, 1942) and found to involve cellular mediation.

On the other hand immunity to viruses has long been recognized as entailing a cellular response. Perhaps because the antigens being poorly defined, the classical means of interplaying antigen and antibody in the laboratory were restricted. Indeed the most dramatic illustration nowadays of the cellular effect is the clinical observation that agammaglobulinaemic children, while they readily succumb to attack by bacteria, have apparently normal resistance to measles, mumps, poliomyelitis, and the virus diseases. Yet humoral antibodies to viruses also exist and are now, for instance, widely utilized in tests for response to poliomyelitis vaccines.

Today, therefore, there need be no surprise that transplantation immunity aroused by homografts is not constantly associated with demonstrable antibodies, though in certain circumstances such antibodies may be present. As Medawar (1959) has reviewed, this depends on the roles in the exciting homograft of H-antigens for humoral antibodies and T-antigens for transplantation immunity, for which the determinant tests are not serological but biological.

Second-set response

One of the earliest pieces of evidence favouring the theory that the homograft reaction was immunological in origin was the observation of the "second-set response". A homograft of skin from rabbit A on rabbit B will "take" initially, will become vascularized and will continue to grow with cell-division until about the tenth day, when within a day or so it undergoes rapid necrosis accompanied by intense infiltration with lymphoid cells. If a second graft of A's skin is then applied to rabbit B, the response is much accelerated. There is little vascularization and necrosis sets in early, about the fourth day. This is very reminiscent of the primary and secondary responses to experimental injections of soluble antigens into test animals. Humoral antibody is produced in but low titre following the first injection and takes about 10 days to appear: following a second injection there is within a few days an intense production of antibody—the logarithmic response.

Transplantation immunity

Until recently transplantation immunity appeared to be out of line with the classical immunity, to bacterial antigens for example, in that not only was production of humoral antibody inconstant but it required living cells of the specific donor to evoke the sensitized state manifested by the second-set response. Cells killed by even the least denaturing process, freeze-drying, caused no transplantation immunity. Extracts of tissue were similarly impotent until Billingham, Brent and Medawar (1956a) treated fresh cells as for the extraction of undenatured DNA (deoxyribosenucleic acid) and found that this extract would produce sensitization. This led to speculation that the transplantation-antigens were confined to the nucleus and were part of a DNA-protein complex. However, further refinements of the method of extraction (Billingham, Brent and Medawar, 1958) have permitted the separation of active antigens from DNA, and preliminary assay of the antigenic fraction suggests that their chemical nature is similar to that of cytoplasmic antigens, such as those responsible for the blood groups, amino acid-polysaccharide complexes (Morgan and Watkins, 1959). Antigen prepared in this

way and injected intradermally into sensitized guinea-pigs produced a delayed reaction very comparable to the Mantoux test for sensitivity to Old Tuberculin. Vice versa, transfer of activated cells from lymph nodes of sensitized guinea-pigs intradermally to the donor of the antigen produced a similar response (Brent, Brown and Medawar, 1959).

Template theories

Tissue antigens thus produce powerful responses in a foreign environment. Naturally they produce no such reaction normally in their native environment; any such reaction would constitute auto-immunity. Burnet and Fenner (1949) sought to explain this phenomenon of non-reactivity against self. They marshalled the evidence against the then currently accepted theory of immunity attributed to Haurowitz, Pauling and Mudd. In essence this postulated that the specifity of antibody was determined by its being synthesized against a template of corresponding antigen; that is for the continued production of antibody there had to be continued presence of antigen. But, as Burnet and Fenner pointed out, immunity, particularly to some of the virus diseases, lasts throughout life, and it was inconceivable to them that virus-antigen could persist for so long. This long immunological memory and the phenomenon of non-reactivity against self were not explicable by the direct template theory. Furthermore, they were impressed by the observations of Owen (1945) who had identified that dissimilar bovine twins, sharing a common placental circulation, in later life had circulating erythrocytes not only of their own blood group but also of their twin's. They postulated, therefore, that in embryonic life the cellular system responsible for disposal of effete cells is plastic and will accept and regard as "self" such antigenic determinants as are presented to it: that in consequence it develops biochemical mechanisms transmissible to daughter cells which perpetuate the processes; but that later in the free-living state the same system, now mature and fixed in its habits, will have to treat new antigens not as "self" but as "foreign", so it will then elicit different processes which are also heritable in the cell line as immunity.

Clonal selection theory

Burnet (1959) now regards much of this "indirect template theory" as clumsy. In its place he now elaborates Jerne's natural selection theory. He propounds that for each antigenic determinant the embryonic mammal must develop cells capable of elaborating the corresponding antibody. He presumes that about 10^4 such cells are probably required. The very large degree of diversification necessary must, he believes, be due to randomization and mutation. Given that this is possible in the time and in the available cell-population—and this is a formidable proposition—then each of these cells and the clones arising from them has its future genetically determined. Those that through the process of diversification form antibody capable of reacting with antigenic determinants of the host are suppressed, perhaps killed; thus immunological tolerance of self (and of any other foreign antigen present at the appropriate time in embryonic life) is established. In the free-living state of the animal the presence of a foreign antigenic determinant will no longer suppress, on the contrary it will stimulate the growth of the clone producing the

corresponding antibody. A first exhibition of antigen will result in a "tooling-up" and the animal will be sensitized; a second exhibition of antigen will result in full productive output, which ultimately will subside but will leave the organism ready for further calls on the same cells—that is the immunological memory is also explained.

IMMUNOLOGICAL TOLERANCE

While the earlier indirect template theory of Burnet and Fenner had its deficiencies, it was valuable in stimulating research on immunological tolerance. Billingham, Brent and Medawar (1956b) were able to experimentally confirm what the theory predicted, namely that foetal mice injected, while still *in utero*, with living cells (spleen) of another mouse would in the subsequent free-living state accept homografts from the donor of the injected cells. This "actively acquired tolerance" was defined as representing the *specific* and *systemic* failure of the mechanism of immunological response which is brought about by exposing embryos of very young animals to "antigenic" stimuli, that is to stimuli which would have caused older animals to become sensitive or "immune". It is notable that the very young animal of certain species may be made to exhibit this phenomenon by injection of foreign material post-natally. Woodruff and Simpson (1955) had shown it for rats and Billingham and Brent (1959) have confirmed it for mice. It is probably related to the relative immaturity of the mouse and rat at birth. Woodruff (1958) was not able to get definite evidence of increased tolerance in two human newborn infants, though, as in cattle, so in man dizygotic twins may show rarely red-cell chimaerism and immunological tolerance of each other's skin (Woodruff and Lennox, 1959), presumably having developed tolerance of each other by an early embryonic exchange of cells.

The role of the lymphatic system in immunity and tolerance

One other important feature of such actively acquired (immunological) tolerance is the fact that it can be abolished by the administration to the previously tolerant animal of immunologically competent lymphoid cells of the host type. This is readily performed in the case of mice where closely in-bred strains are so genetically (and therefore antigenically) homogeneous as to be immunologically identical. Thus the tolerance of an A strain mouse injected at birth with tissue from a CBA strain mouse, confirmed by its carrying a homograft of CBA skin, can be abolished by the intraperitoneal injection of cells from some 12 or more lymph glands of a normal adult A mouse (Billingham, Brent and Medawar, 1954, 1956; Mitchison, 1957). (This quantity probably represents some tens of millions of lymph cells.) These mature lymphoid cells will be accepted by the A host; they will recognize the CBA antigen in the tolerant mouse and be stimulated to action which in their case is the immunological response, so that the CBA skin will now be shed. Presumably they also react and kill the CBA cells injected at birth to produce tolerance, for it now seems established that persistence of such living cells with their specific antigens is a necessary requisite for the maintenance of tolerance (Mitchison, 1959).

The lymphatic system has of course long been recognized as being associated with the immunological defences of the body; but lymphatic tissue contains a

mixed population of cells. Formerly there was considerable disagreement about which were the cells effecting the immunological response. Small lymphocytes which are plentiful in number but obscure in function were favoured by Dougherty (1952) and his co-workers, plasma cells or their precursors by Fagraeus (1948). Due largely to the elegant use of fluorescent antibodies by Coons, Leduc and Connolly (1955) the general opinion now is that the plasma cell series is the source of antibodies. However, as formerly, soluble antigens have mainly been used for immunization. In the Coons test antigen is applied to frozen sections of lymphatic tissue and the sites of absorption *in vitro* determined by a precipitin reaction with the fluorescein-labelled antibody. It would be instructive to repeat this procedure with tissue antigens, now that at any rate crude preparations of T-antigens are available, to ascertain whether these T-antigens are, like H-antigens, specifically attracted to plasmatoid cells or whether the classical lymphocyte-series is involved in this response.

Production of cells of the lymphocyte-series seems to be confined to lymphatic tissue. Production of plasmatoid cells may, however, occur as well in other sites where primitive mesodermal tissue can be stimulated. An example is perhaps the antibody-producing granuloma following injection of antigen precipitated with aluminium phosphate (White, Coons and Connolly, 1955). Another example is the bone marrow which normally contains plasma cells and in which plasmocytomas arise.

REDUCTION OR ABOLITION OF IMMUNOLOGICAL REACTIVITY

Non-specific physical and chemical methods

The lymphocyte series of cells is extremely sensitive to ionizing radiation and is thus readily eliminated for a time. Mature plasma cells are relatively resistant to radiation and the whole series may be less affected than the lymphocytic series. By giving animals substantial doses of x-rays (say 400 roentgen (r)) the primary response to a soluble antigen given a few hours later can be abolished. Taliaferro (1957) found, however, a latent period of an hour or so after the irradiation during which H-antigen in the form of heterologous red cells can be given with some effect and, if the antigen is given a day or so before the irradiation, the immune response is even greater than normal. Moreover the diminished response to antigen given one day after 400r can be restored by the supplementation of antigen with certain products of nucleoprotein. The secondary response to antigen is delayed and depressed but far from inactivated. The antibody-productive mechanism is therefore not completely knocked out by radiation as are the lymphocytes; it seems that it is mainly the inductive process that is disordered. It would be valid to speculate in this context, like Burnet (1959) in another, that the lymphocyte is the carrier of the antigen. Burnet supposes that antigen attaches itself to lymphocytes of the clone appropriate for the determinant groups; the lymphocyte then either itself de-differentiates to form a stem-cell or stimulates other primitive cells of its own clone to divide and produce antibody through the plasma-cell-series. Even after a moderately large dose of radiation the efferent path of this cycle would be operative, but the afferent path initiating sensitization

corresponding antibody. A first exhibition of antigen will result in a "tooling-up" and the animal will be sensitized; a second exhibition of antigen will result in full productive output, which ultimately will subside but will leave the organism ready for further calls on the same cells—that is the immunological memory is also explained.

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so long as the antigen remains detectable. In this respect it resembles immunological paralysis, but it differs in that it appeared not to be due to simple neutralization of antibody as formed.

(4) The phenomenon of the radiation-chimaera (Ford and his colleagues, 1956) produced by lethally irradiating animals, their recovery being permitted by the intravascular administration of foreign haemopoietic cells which recolonize the aplastic haemopoietic and lymphopoietic tissues of the host.

Medawar groups these conditions in the present state of incomplete knowledge into two broad groups—the tolerant states of essential non-reactivity (immunological tolerance, the Sulzberger-Chase phenomenon and prolonged non-reactivity produced by whole-body irradiation) and the thwarted reactivities of immunological paralysis and protein overloading. In discussing the former states he speculates that, if the evocation of adaptive enzymes is pertinent to the mechanisms of immunity, it is more likely to operate for tolerance than for antibody formation; in this case immunological tolerance could represent an enforced retention into adult life of enzymes which catabolize antigens too rapidly for antibodies to be formed.

In the present context we are concerned in considering whether homografting can ever become a practical proposition. Therefore, true immunological tolerance induced in foetal life can have little application, though, it is true, if we can but elucidate all the mechanisms involved, this fundamental knowledge can be helpful in an approach. *It should be noted that so far we have two suggested hypotheses* to account for the phenomenon—suppression and perhaps extinction of clones specifically reactive for the relevant antigenic determinants (Burnet), and the production of adaptive enzymes enabling immediate degradation of antigen (Medawar, following Burnet and Fenner).

It is therefore meet to consider the two other states of essential immunological non-reactivity.

SULZBERGER-CHASE PHENOMENON

Landsteiner (who has fathered so much immunology) and Chase (1942) had shown that dermal sensitivity of the delayed type to simple organic compounds could be transferred from one animal to another within a species by cells but not by serum. Further work has been reviewed by Chase (1953), showing that such secondary hosts have acquired an anaphylactic state—a positive Schultz-Dale test is obtained—so that exo-antibody is also involved as a by-product.

Guinea-pigs, which regularly may be made sensitive by intracutaneous injections of a compound (such as 2:4 dinitrochlorobenzene), can be made resistant to such sensitization by the prior feeding of the compound in olive oil (Chase, 1946). *Such resistant* animals are also resistant to anaphylactic sensitization with conjugates made from the same chemical and guinea-pig protein. If the appropriate antibody is passively given to the resistant animals, it is cleared from the circulation at the same rate as in normal animals. Had a state like Felton's immunological paralysis been responsible for the resistance, one would have predicted an accelerated rate of clearance due to a "mopping-up" of antibody by depots of antigen. Furthermore, these resistant animals after subjection to procedures

would depend on the presence of intact lymphocytes (or their specific principles and this would be limited to a period of an hour or so (*see* Trowell, 1958).

Induction of sensitization to T-antigens is also delayed and depressed by radiation according to Dempster, Lennox and Boag (1950), whose homografts of skin were shed more slowly in irradiated than in normal rabbits. The primary grafts having necrosed the irradiated rabbits then had normal second-set responses, but the effect of irradiating a sensitized rabbit to test the response to a subsequently applied homograft was not scored. Instead they (Lennox, Dempster and Boag, 1952) irradiated rabbits sensitized to tubercle bacilli and noted their response to Mantoux tests. They were surprised to find these suppressed and attributed the result to adrenocortical stimulation rather than to loss of lymphocytes. In the light of present knowledge the latter would seem more likely.

Certainly the effects of radiation on the immune response to both H-antigens and T-antigens are non-specific and are to be contrasted with the specificity of the induction of antibody by antigen or of the induction of immunological tolerance by antigen. Chemical agents which are cytotoxic, such as the mustard gas derivatives and natural hormones like hydrocortisone, are similarly non-specific in that they act on cells of all the available clones, even though they produce their end results by different means. It is not justifiable to use the term immunological tolerance in describing the action of any of them until specificity has been demonstrated. Recently one such agent, the antimetabolite 6-mercaptopurine (6-MP), a non-specific purine antagonist, has been shown by Schwartz, Eisner and Dameshek (1959) to abolish the primary but not the secondary response to H-antigen. Its action certainly seems to be central so that in terms of the hypothesis above it must block the de-differentiation of the antigen-bearing lymphocytes or preclude their stimulating stem cells of the same clone. Furthermore, and this makes it more interesting, an H-antigen (bovine serum albumin—BSA) given during blockade by 6-MP results in later specific insensitivity to BSA but not to bovine *gamma*-globulin: thus immunological tolerance is strongly suggested (Schwartz and Dameshek, 1959).

Specific states

In contrast to the non-specific reduction or abolition of immunological reactivity by physical and chemical methods, there are states which are specific. Medawar (1960) has reviewed the present situation as regards several of them *vis-à-vis* the immunological tolerance produced by exposure to antigen very early in life, a subject already reviewed by Brent and Medawar (1959). These can be listed in historical order.

(1) The Sulzberger-Chase phenomenon is the specific abolition of the ability of guinea-pigs to develop delayed cutaneous supersensitivity to certain chemicals by the prior administration by mouth of that substance.

(2) Felton's (1949) immunological paralysis is the specifically unresponsive state manifested in mice following the administration of a very large dose of pneumococcal polysaccharide which in smaller doses elicits vigorous production of antibody.

(3) The immunological unresponsiveness of Dixon and Maurer (1955) caused by exposing adult rabbits to very high doses of soluble protein antigens. This lasts only

weeks after the irradiation, soon shows delayed ill-effects and often dies within 2–3 months (Barnes and Loutit, 1955)—the so-called "secondary disease".

Secondary disease and runt disease

This secondary disease of the radiation-chimaera is, in its clinical and histological manifestations, very similar to the "runt disease" described by Billingham and Brent (1959) in the homologous chimaera formed by injecting the newborn mouse with homologous spleen-cells to induce immunological tolerance. Just as Billingham and Brent attribute "runt disease" to a reaction by the multiplying immunologically competent lymphoid cells in the donated suspension of spleen against the host which tolerates them, so "secondary disease" of the radiation chimaera has been credited as due to the reaction of the colonizing foreign haemopoietic cells against their host (Barnes and his colleagues, 1957; Uphoff, 1957). It has also, however, been attributed to recovery on the part of the host with reaction against the colonizing cells (Mackinodan, 1957).

These counter-claims identify the fact that chimaeras of all kinds involving haemolymph tissue present considerable difficulties. Theory permits the host to react or to be non-reactive immunologically against the graft and similarly for the graft against the host. In Billingham and Brent's case the newborn host is immunologically unreactive; it has an extremely immature lymphoid system and has a physiological demand for an immunological defence system. There is thus a situation which will encourage the multiplication of lymphoid elements. Giving mature spleen cells from a foreign host initiates a contest. If the mature donated tissue prevails at the expense of the immature host-tissue, it is likely to be sensitized by the host's antigen, to react against it and to cause runt disease. The animal dies tolerant of the tissue which kills it. But not all such chimaeras die, or even manifest runt disease clinically, though probably minor features are present. This may be because the host's lymphoid tissue has some unexplained advantage over the more mature donated cells and overgrows them. Provided the host remains tolerant of the donated cells it cannot eliminate them by immunological means but it can crowd them out so that they become an inconspicuous and ineffective minority. The author's colleagues, Barnes and Ford (unpublished), have shown this under the following circumstances. An A strain newborn mouse was injected intravenously with cells from the F_1 (CBA × T6)—T6 being a line of mice with a cytologically identifiable marker-chromosome. When adult, this A mouse was shown to be tolerant since it accepted a homograft of CBA skin. It was then sacrificed and used as a donor of haemopoietic tissue for lethally irradiated CBA mice. No dividing cells with the T6 marker could be found on cytological examination of the A mouse, but when the irradiated CBA mice were sacrificed a month or so after recovery due to this injection of A cells, their haemopoietic tissues had many dividing cells containing the marker-chromosome. They must surely have been crowded out in the A environment, and could only express themselves and gain dominance when transferred to a CBA environment.

"Partial immunity"

We have thus, with the Billingham-type chimaera, either obvious and lethal immunological reaction against the host on the one hand or non-reaction on the

normally causing sensitization, when used as donors of lymphoid cells, could not transfer any supersensitivity to secondary hosts. This also indicates a non-function, not a thwarting of their processes of immunity. However, this induced non-function does not prevent the particular animal being made sensitive when it is made passively to adopt lymphoid cells from a sensitized animal (Battisto and Chase, 1955).

The tentative conclusion must be that the clones of cells capable of giving the dermal sensitivity have been so suppressed or their metabolic activities so altered by the experimental procedures that they can no longer be shown to manifest the specific phenomenon.

THE RADIATION-CHIMAERA

Considerable attention has been given to the radiation-chimaera in recent years. Most of the experimental work has been carried out on mice, though rats, rabbits and dogs have also been used, and some information is being derived from man.

For mice data will be given for one strain, namely the inbred CBA strain. Hybrid animals may be rather tougher in general but it is valuable to consider homogeneous strains for genetic reasons as will become obvious. The facts at present known are as follows: 250-kilovolt x-radiation given at high intensity (about 40r per minute) causes death within some 3-5 days from damage to the intestinal mucosa following accumulated doses of 1,500r and upwards; with doses of about 1,000–1,500r the damage to the gut is not spontaneously irremediable as it is with the higher doses, but the haemopoietic tissues, myeloid and lymphoid, are destroyed and this in untreated animals is also uniformly lethal (LD_{100}) within about 10–14 days; doses of 750–1,000r are in the lethal range, the probability of death within 30 days varying according to the dose, the median (LD_{50}) being about 850r.

Mice given the LD_{100} may nevertheless recover following treatment—the intravenous injection of cell-suspensions of haemopoietic tissue, bone marrow from adult mice (Lorenz, Congdon and Uphoff, 1952), spleen from infant mice or foetal liver or spleen (Jacobson, 1952). It is notable that so far no therapeutic success has been claimed for suspensions of purely lymphoid cells. It is now known that recovery is dependent on the recolonization of the depopulated haemopoietic tissues by the donated cells (Ford and his colleagues, 1956) and this holds for rats (Lindsley, Odell and Tausche, 1955) and rabbits (Porter, 1957). Dogs differ in that they are initially recolonized but do not recover for a variety of reasons (Porter and Couch, 1959; Thomas and his colleagues, 1959). If the donated cells are those previously withdrawn from the recipient himself (autologous) or those from another animal identical genetically (isologous), the ultimate results in terms of longevity are extremely satisfactory (Barnes and Loutit, 1959). Isologous CBA/CBA radiation-chimaeras induced when the host-mouse is about 100 days of age live for a median period of a further 500 days. However, if the donated cells are from a different strain of mouse (homologous), the results are frequently very much less satisfactory as far as late results are concerned. The animal, though it survives the period of the radiation syndrome, the first few

the recovered chimaera stem from the supplanting donor. In the ordinary course of physiological processes host's antigens are carried to the lymph tissues where they react immunologically *in situ* with the donor-derived lymphoid cells. Thus, if the reaction is severe, mutual destruction occurs resulting in loss of the lymphoid tissue.

Modifications of the phenomenon

This relatively straightforward picture becomes modified if mice are given not the LD_{100} dose of x-rays, but some dose rather less. Trentin (1956) and also Cohen, Vos and van Bekkum (1957) have shown that mice given doses somewhat less than the LD_{50} do not have an improved chance of survival when treated with homologous or heterologous bone marrow; in fact, the reverse is the case. All the mice may die instead of more than half surviving. The evidence presented by Congdon, Makinodan and Gengozian (1957) is convincing that such mice treated with rat bone marrow are initially recolonized by rat cells, which are then destroyed presumably by a recovery of the host's own immunological mechanisms. This destroys the graft on which the animal is vitally dependent.

However, a still different phenomenon may occur following doses of x-rays between the LD_{50} and LD_{100}. Our own evidence (Barnes and his colleagues, 1959a) is that, while some recovered animals ultimately have a reversion of their haemopoietic tissues completely from the donor-type (rat) to host-type (mouse) cells, presumably a delayed and weak host versus graft reaction, others may manifest a partial reversion. Their myeloid tissues and such lymphoid tissue as remains had mitotic cells of both rat-type and mouse-type chromosomal constitution. They also retained grafts of rat skin. In these animals the host tissue has recovered from the suppression induced by the radiation; myeloid and lymphoid tissue has been formed, but it is capable of so little immunological reaction against the donor tissue that both live and divide symbiotically. The relative sizes of the populations of rat and mouse cells seem determined by their respective physiological abilities, the one being appropriate for the environment and impaired by its previous radiation damage, the other being foreign but not damaged by radiation. This is a situation which bears the hallmarks of immunological tolerance of the host for the graft in that the cellular system of the host has reformed from basic reticulo-endothelial stem-cells in the continued presence of foreign cells, just as induced tolerance in the sense of Billingham, Brent and Medawar (1956) was effected by the presence of foreign cells in the normal evolution of the immunological mechanism from embryonic reticulo-endothelium.

The evidence that the recovered lymphoid tissue is in fact derived from primitive undifferentiated stem-cells also comes from cytological observations on many of the same animals. The murine cells often show the scars of their previous radiation lesions in the form of chromosomal translocations. These translocations are distinctive and each is virtually unique. Cells having the same recognizable translocation must all be members of a clone which arose from a single mother cell bearing this anomaly. Cells of the same clonal type can be identified in bone marrow, spleen, lymph nodes and thymus, and often several different clonal types are each recognizable in all these various tissues. Thus the animals'

other hand, presumably due to suppression of mitosis. In both cases the host is tolerant of the donated cells and retains them. However, not all combinations of host and donor show this persistent tolerance. Billingham and Brent (1957) recorded a number of combinations where tolerance is only transitory and the host ultimately develops an immunological reactivity against the donated cells and eliminates them. This has been referred to as "partial tolerance" and in the first instance it may well be so. Ultimately, however, tolerance is abolished and while subsequent immunological reactivity of the host towards further exposure to donor antigens may not be as strong as normally, it is hard to conceive of this as partial tolerance: it is rather "only partial immunity".

Histology

In the radiation chimaera we have different circumstances in the first instance. The host's myeloid and lymphoid tissues have been completely destroyed by the radiation and no lymphoid cells survive. What is left is the reticulo-endothelial framework of both tissues. If the dose of radiation has been sufficiently great (LD_{100}), in our experience regeneration of host-type myeloid and lymphoid tissue occurs only very rarely. The injected myeloid cells can colonize the vacant spaces of these nets and, in fact, the normal histology of the myeloid tissues is restored first (Barnes and Loutit, 1956); regeneration of lymphoid tissue follows, but even in the most favourable circumstances—colonization by isologous cells—this may be suboptimal, and in unfavourable situations—restoration with certain foreign cells—pathological features are seen at a very early stage (Congdon and Urso, 1957). In the unfavourable case the end-result is, for instance, a lymph node with no recognizable lymphoid tissue at all; reticulo-endothelial cells survive here and there in a matrix of hyaline material.

Cytological findings

Our cytological findings (Ford and his colleagues, 1956, 1957) reinforce the histological findings. When homologous myeloid tissue from the T6 line containing the marker-chromosome is given to CBA mice, initially there are abundant mitotic figures to score in both myeloid and lymphoid tissues. Following the LD_{100} dose of radiation to the CBA host, these mitotic figures invariably contain the marker-chromosome of the donor in both tissues. Empirically it has been found that "secondary disease" is of comparatively mild form in this combination and many mice are long-lived. The myeloid tissue continues to be mitotically active throughout life and the T6 marker-chromosome persists as the sole cell-line; but the lymphoid tissue becomes atrophic and provides only few mitoses, which when present are also of the T6 type. By the cytological technique, only cells in division can be identified as of one or the other population, but in heterologous chimaeras (irradiated mice restored with bone marrow from rats) Brocades Zaalberg and van Bekkum (1959) have demonstrated rat lymphocytes in the lymph tissue by immunological methods.

Our interpretation (Barnes and his colleagues, 1957) of the findings in homologous chimaeras has been that, as a result of the irradiation, the host's own myeloid and lymphoid tissues are permanently destroyed and the active tissues of

with homologous CBA bone marrow, by means of either normal or sensitized lymphoid cells ($\sim 10^7$ intravenously). However, in these circumstances not only was the radiation dose different, but the donor-host relationship was homologous and not what we (Barnes and his colleagues, 1958) have termed semi-isologous—that is, parent strain versus F_1 and vice versa.

Relationship of grafted haemopoietic tissues versus the host

This raises the problem once again of the relationship of the grafted haemopoietic tissues versus the host. It has been noted that we regard delayed death in the second-fourth month of homologous and heterologous chimaeras to have been initiated by a reaction of the now immunologically competent graft cells against the host. The reasons for this belief were summarized (Barnes and his colleagues, 1958) as follows.

(1) The myeloid tissue of donor origin is unaffected according to histological evidence. Only the donor-type lymphoid tissue is destroyed (*see* above). Both should be affected in a host against graft reaction.

(2) The semi-isologous situation is a potent method for investigating the matter. The F_1 hybrid between two pure strains has in heterozygous combination all dominant antigens of both parents and therefore in theory cannot react immunologically against either, while each parental type is capable of reacting against the antigens of the other parent present in the F_1. Uphoff (1957) elegantly exploited this two-way situation with many combinations of pure strains and showed that, while secondary disease and death were common following administration of parental marrow to the irradiated F_1, it was rare when F_1 marrow was given to the irradiated parent. Trentin (1958) and ourselves (Ilbery, Koller and Loutit, 1958) have reported similarly though less comprehensively. The most convincing individual demonstration was reported by Uphoff and Law (1958), whose two parental lines C57BL(H-2^b) and C57BL(H-2^d) differed by only one gene, albeit the vitally important H-2 gene which plays a leading role in histocompatibility: pronounced secondary disease occurred when C57BL(H-2^d) marrow was given to the irradiated F_1 but not when F_1 marrow was given to the irradiated parent. The arrangement indicates reaction of graft against host.

(3) When a homologous or heterologous chimaera bearing a graft of donor's skin dies of secondary disease, one would expect to find some lesion in the graft if the cause of death is a host against graft reaction, but clinically and histologically such grafts are immaculate.

(4) The similarity with "runt disease" as scored by Billingham and Brent (1957, 1959) is remarkably close. In this case the host is tolerant of the graft, so that any immunological reactivity is in the direction graft against host.

(5) In established heterologous chimaeras of mouse and rat, examination of the animals' sera has revealed rat-type serum proteins—especially *gamma*-globulins (Grabar and his colleagues, 1957; Weyzen and Vos, 1957). The test reagents were anti-rat sera from rabbits or chickens. However, when mouse anti-rat sera are used, rat serum proteins have not so far been detected (Makinodan 1957; Gengozian, 1959), presumably because this is a most insensitive system.

(6) If secondary disease is due to the graft's reactivity against the host, theory

total myeloid and lymphatic complement of murine cells is probably derived from some two, three or very few more viable clone mother cells (Barnes and his colleagues, 1959b).

The picture therefore emerges that, depending on the dose of x-rays given to the mouse before injection of myeloid tissue for recolonization, one may get (1) only temporary inactivation of the immunological ability to reject the foreign cells and therefore a later host versus graft reaction; (2) a permanent immobilization of the immunological capacity to reject the graft, but only temporary inactivation of the mitotic capacity of certain mesenchymal stem-cells, leading to a state like immunological tolerance; and (3) a permanent immobilization of the putative stem-cells and therefore an immunological non-reactivity.

Differences between laboratories

This is the deduction from work carried out largely within our laboratory. It is not always easy to transpose the work done in different laboratories. Although the strains of mice used may bear the same varietal name like CBA, and though they originally stemmed from a single origin, it is well known that genetic variation must necessarily occur with time. Thus the CBA mouse of the Harwell strain conforms to type in one of the most important transplantation antigens, but the CBA strain used in the Netherlands is different (Gorer—personal communication). Different standards of hygiene and nutrition between laboratories will also cause differences in radiosensitivity. Thus the mean lethal dose for the Harwell CBA is 850r but, for the local CBA strain used by Trentin in Houston, it is 550r. It is doubtful if differences in physical measurements between laboratories could account for more than a variation of a few per cent. If absolute dose, rather than dose relative to LD_{50} or LD_{100} is crucial, then differences in results and interpretation between laboratories is understandable.

Immunological tolerance to the graft

With this in mind one can reconsider the question as to whether the irradiated animal can exhibit true immunological tolerance to the graft. It is well established, of course, that these radiation-chimaeras will accept grafts of skin of the donor-type. The first report of this was from Main and Prehn (1955), who irradiated DBA mice, effected recovery with myeloid tissue from the F_1 hybrid of DBA and BALB.c and then obtained acceptance of the skin from BALB.c. Trentin (1956) has confirmed the observation with different strains and so have we (Barnes and Loutit, 1959). If this is due to immunological tolerance on the part of the host, then it should be abolished by the injection into the chimaera of host-type lymphocytes, either from a normal animal or more rapidly from one immune to donor-type tissue. Trentin (1958) reported that Cb. skin is shed from an irradiated (770r) CBA, restored with Cb.$\times$CBA bone marrow, by giving lymphocytes from a normal CBA mouse, often with death of the animal from anaemia and haemorrhage. As Trentin pointed out this may indicate the abolition of a previous state of immunological tolerance of the host or that the immune mechanism of the chimaera was previously determined entirely by colonizing donor cells. On the other hand, in our laboratory, we (Micklem, unpublished) have been unable to shift donor-type skin grafts from irradiated A mice (950r), restored

massive *homograft reaction.* When a hybrid between two pure strains is parabiotically united to a parent-type animal, it is the hybrid, with initially the greater physiological vigour, that dies wasted (van Bekkum, Vos and Weyzen, 1959). Parabiosis permits not only the transfer of humoral agents including soluble antibodies between the two, but the common circulation allows passage of immunologically competent cells. What the respective roles of sensitized cells and humoral antibodies are in the parabiotic intoxication is still to be determined.

A less overwhelming and continuous bombardment is effected by injecting normal F_1 animals with cells from a parent-type animal. Trentin (1959) has noted death of weanling F_1 mice from intraperitoneal injection of parental lymphoid cells, but no ill-effects seemed to follow if the injected F_1 mice were more mature: parental cells of one type tended to be more effective than those of the other. Cole and Ellis (1958), perhaps by a fortunate choice of strains, did kill adult F_1 mice with parental type lymphoid cells and more readily and earlier if the F_1 mice had been sublethally irradiated beforehand. It would seem that mature mice are more or less able to suppress the function and, probably also, the ability to multiply of host compatible semi-isologous lymphoid cells. By definition this suppressing action cannot be an immune response, but as with the immune response so also is this suppressor weakened by prior irradiation of the host. Even when lymphoid cells from a parental-type mouse immunized against the other parent are injected into an unirradiated F_1 host, the results are not predictable. Gorer and Boyse (1959) found that, when tissue from one immune parent was used, death was even more certain than with normal lymphoid tissue, but to tissue from the other immune parent the F_1 host was still fully resistant. The theoretical suppressive potency of the F_1 host must have been very great. Alternatively, there is the explanation of Gorer and Boyse themselves, that some parental immune cells may by their genetic nature be unduly susceptible to allergic death on meeting the appropriate antigen: but this makes their proved initial colonization hard to explain.

Interpretation

These observations on graft versus host reactions in a normal environment do help us to interpret the situation in homologous and perhaps in heterologous radiation-chimaeras. While the environmental host is atypical, and may as we have seen, depending on the radiation-dose it has received, be immunologically infirm or tolerant or deficient, the graft has in the first few weeks to undergo great *physiological development. It has to expand to supply all the myeloid and lymphoid* functions of the animal. Its myeloid tasks seem to be relatively uncomplicated and it rapidly completes them. Its lymphoid development depends on its source.

If the graft contains immunologically competent lymphoid tissue in addition to myeloid, for example, adult and even infant spleen, the expanding lymph tissue can be readily sensitized by the available host's antigens. It has little or no opportunity to exhibit anything like immunological tolerance or to develop adaptive enzymes for immediate disposal of host's antigen. It would be expected, therefore, to stage a brisk and increasing immune response against the host, which by virtue of its radiation-debility must also have little left of any postulated suppressive

suggests that the use of foetal rather than adult tissue might permit the exercise of some immunological tolerance in the reaction. Barnes, Ilbery and Loutit (1958) and Uphoff (1958), have indicated that in certain circumstances secondary disease is precluded or diminished by the use of foetal material. Further experience in our laboratory shows that giving donor material from C57BL foetal mice to lethally irradiated CBA mice results in a substantial proportion of chimaeras living for up to a year while those formed from adult bone marrow all die within four months (Barnes, Loutit and Westgarth, 1959); and still greater longevity is attained in similar recipients given foetal tissue from mice of strain A (Barnes and his colleagues, unpublished). Whether this is immunological tolerance in the strict sense of the term has still to be ascertained. Simonsen and Jensen (1959) have evolved a method of assay in which spleen cells of the animal to be tested are injected intraperitoneally into newborn mice. These are sacrificed after 10 days; a positive reaction is indicated by splenomegaly. In tests to date (unpublished observations) spleen cells from CBA/A (foetal) chimaeras injected into newborn CBA mice have not given splenomegaly, suggesting that the A cells are in fact non-reactive against CBA antigens. On the other hand CBA/A (foetal) chimaeras injected intravenously with 10^7 lymphoid cells from both normal A mice and A mice immune to CBA have not shown any remarkable change, which would be expected if the A graft tissue in the chimaera were immunologically tolerant of CBA. The non-reactivity of the donor-tissue against the host in these animals appears to be affirmed but its exact nature is still problematical.

Feldman and Yaffe (1958) have also been interested in the reactivity and non-reactivity of the graft against the host. When irradiated C3H mice were restored with spleens from C57BL infants, they developed secondary disease. However, if such mice were sacrificed early on the twelfth day and lymphoid cells were transferred to normal C57BL hosts, these secondary hosts developed within five days potent anti-C3H haemagglutinins in their serum. This is a convincing demonstration of immunity adopted from the graft tissue of the chimaera. Furthermore, these workers have independently identified a reduced reactivity of graft against host following the use of foetal liver for restorative therapy. Not only is the reaction against the host minimized, but as they (Feldman and Yaffe, 1959) showed later, such chimaeras are less able to throw off foreign tumours. These experiments do not, however, confirm that the reduction of reactivity is in virtue of true immunological tolerance.

Graft versus host reactions in a normal environment

The graft versus host reaction having been recorded (and reviewed by Medawar, 1958) in these rather special circumstances of "runt disease" and "secondary disease", there have naturally been efforts to elucidate what happens in more orthodox situations. Parabiosis—the surgical union of two individuals—cannot strictly be regarded as orthodox, but it has long been recognized that such union, except in identical twins (spontaneous in Siamese twinning in man) or between highly inbred animals, results in early death of one partner—once called parabiotic intoxication (Finerty, 1952). There is now every reason to believe that this is a

in severity of "secondary disease" of the radiation-chimaera must be due to a suppression of immunological activity on the part of the graft associated with its initial immaturity, though not necessarily true immunological tolerance. A fuller understanding of this is certainly needed.

REFERENCES

Albert, F., and Lejeune-Ledant, G. (Ed.) (1959). *Biological Problems of Grafting*. Oxford: Blackwell.
Barnes, D. W. H., and Loutit, J. F. (1955). In *Radiobiology Symposium 1954*. p. 134. Ed. by Bacq, Z. M., and Alexander, P. London: Butterworth.
— — (1956). In *Progress in Radiobiology*. p. 291. Ed. by Mitchell, J. S., Holmes, B. E., and Smith, C. L. Edinburgh: Oliver and Boyd.
— — (1957). *Brit. J. haem.*, **3**, 241.
— — (1959). *Proc. roy. Soc. B.*, **150**, 131.
— Ilbery, P. L. T., and Loutit, J. F. (1958). *Nature, Lond.*, **181**, 488.
— Loutit, J. F., and Westgarth, D. (1959). *Gerontologia*, **3**, 137.
— Ford, C. E., Gray, S. M., and Loutit, J. F. (1959a). In *Biological Problems of Grafting*. p. 274. Ed. by Albert, F. and Lejeune-Ledant, G. Oxford: Blackwell.
— — — — (1959b). In *Progress in Nuclear Energy, Series VI. Biological Sciences*. Vol. 2, p. 1. London: Pergamon Press.
— — Ilbery, P. L. T., Koller, P. C., and Loutit, J. F. (1957). *J. cell comp. Physiol.*, **50** (Suppl. 1.), 123.
— — — and Loutit, J. F. (1958). *Transplant. Bull.*, **5**, 101.
Battisto, J. R., and Chase, M. W. (1955). *Fed. Proc.*, **14**, 456.
van Bekkum, D. W., Vos, O., and Weyzen, W. W. H. (1959). *J. Nat. Cancer Inst.*, **23**, 75.
Berrian, J. H., and Brent, L. (1958). *Ann. N. Y. Acad. Sci.*, **73**, 654.
Billingham, R. E., and Brent, L. (1957). *Transplant. Bull.*, **4**, 67.
— — (1959). *Phil. Trans. B.*, **242**, 439.
— — and Medawar, P. B. (1954), *Proc. roy. Soc. B.*, **143**, 58.
— — — (1956a). *Nature, Lond.* **178**, 514.
— — — (1956b). *Phil. Trans. B.*, **239**, 357.
— — — (1958). *Transplant. Bull.*, **5**, 377.
Brent, L., and Medawar, P. B. (1959). In *Recent Progress in Microbiology*. p. 181. Stockholm: Almquist and Wiksell.
— Brown, J. B., and Medawar, P. B. (1959). In *Biological Problems of Grafting*, p. 64. Oxford: Blackwell.
Brocades Zaalberg, O., and van Bekkum, D. W. (1959). *Transplant. Bull.*, **6**, 91.
Burnet, F. M. (1959). *The Clonal Selection Theory of Acquired Immunity*. London: Cambridge University Press.
— and Fenner, F. (1949). *The Production of Antibodies*. 2nd ed. Melbourne: Macmillan.
Chase, M. W. (1953). In *The Nature and Significance of the Antibody Response*. p. 156. Ed. by Pappenheimer, A. M., Jr. New York: Columbia University Press.
— (1946). *Proc. Soc. exp. Biol.* N. Y., **61**, 257.
Cohen, J. A., Vos. O., and van Bekkum, D. W. (1957). In *Advances in Radiobiology*. p. 134. Ed. by Hevesy, G. C. de, Forssberg, A., and Abbatt, J. Edinburgh: Oliver and Boyd.
Cole, L. J., and Ellis, M.E. (1958). *Science*, **128**, 32.
Congdon, C. C., and Urso, I. S. (1957). *Amer. J. Path.*, **33**, 749.
— Makinodan, T., and Gengozian, N. (1957). *J. Nat. Cancer Inst.*, **18**, 603.
Coons, A. H., Leduc, E. H., and Connolly, J. M. (1955). *J. exp. Med.*, **102**, 49.
Dempster, W. J., Lennox, B., and Boag, J. W. (1950). *Brit. J. exp. Path.*, **31**, 670.
Dixon, F. J. and Maurer, P. M. (1955). *J. exp. Med.*, **101**, 245.
Dougherty, T. F. (1952). *Physiol. Rev.*, **32**, 379.
Fagraeus, A. (1948). *Acta med. scand.*, **130**, 204.
Feldman, M., and Yaffe, D. (1958). *J. Nat. Cancer Inst.*, **21**, 697.

powers. In practice it is found that adult homologous spleen produces earlier death from secondary disease than bone narrow (Makinodan, Gengozian and Shekarchi, 1958). Giving spleen or bone marrow plus lymph glands from a pre-immunized donor leads to a very early death—presumably an accelerated reaction (Barnes and Loutit, 1957). The histology of the lymphatic tissues is then very striking. Lymph nodes show not atrophy but hyperplasia with large mononuclear cells of the "transitional" type (Ilbery, Koller and Loutit, 1958); it is relevant to speculate whether this indicates production of humoral iso-antibody cytotoxic to the host.

If the graft is of homologous bone marrow, reformation of the lymphoid tissues is slow. It is still undetermined whether the lymphoid tissues are repopulated from a pluripotent stem-cell of the marrow which can develop either into myeloid cells in an environment of marrow or splenic pulp or into lymphoid cells in a lymphatic environment, or whether the small lymphocytes always found in marrow can de-differentiate to lymphoblasts (Loutit, 1960). In either case final development must occur from a relatively immature cell-population and at this stage of immaturity the host's antigens might be able to induce some degree of immunological tolerance. Our present deduction, however, is that we have not seen true tolerance or facilitated the expression of adaptive enzymes. It is true that, as with the Billingham type of chimaera, by selecting grafts on the basis of histocompatibility with host at the H-2 locus one can get diminishment of the secondary disease (Barnes and his colleagues, 1957). Uphoff and Law (1959) have shown this quite convincingly and indicated that compatibility at the H-1 locus may also be a factor, though the H-3 seemed less important. This may imply that suppression of reactivity against host antigen is possible in the recovering host if the antigenic stimulus is weak. It could also be explained as clonal selection. The reacting clones could be eliminated by contact with antigen; and with a slow and not too violent reaction, time might be allowed for mutant non-reacting clones to develop and take over other essential lymphoid functions.

Where secondary disease of the radiation-chimaera differs from "runt disease" in the infant chimaera of Billingham and Brent (1959), is that in the infant case reaction of the graft (injected splenic cells) against the host can be greatly diminished by utilizing cells from bone marrow as the agent for inducing tolerance in the host. While marrow contains a considerable proportion of small lymphocytes in its population it has no lymphopoietic foci. It can be argued that marrow is the graveyard of small lymphocytes (Loutit, 1960). Thus for marrow to be a source of immunologically competent cells one has to invoke totipotent stem-cells. The time taken for these to mature will be extensive. In the case of the infant mouse the host's own lymphoid tissue will have developed and matured during this interval and is likely to have won any postulated physiological contest (*see* above). In the radiation chimaera, however, there is no competitive lymphoid tissue of the host, so in spite of a time-lapse the donor-type lymphoid tissue can ultimately express itself and react against the host.

When the graft is originally of foetal tissue, reaction of the graft against the host is diminished. This applies also for "runt disease" and the same argument as used in the preceding paragraph holds good in this situation also. The diminution

Weyzen, W. W. H., and Vos, O. (1957). *Nature, Lond.*, **180**, 288.
White, R. G., Coons, A. H., and Connolly, J. M. (1955). *J. exp. Med.*, **102**, 73.
Woodruff, M. F. A. (1958). In *La Biologie des Homogreffes*. p. 261. Paris: Centre National de la Recherche Scientifique.
— and Lennox, B. (1959). *Lancet*, **2**, 476.
— and Simpson, C. O. (1955). *Brit. J. exp. Path.*, **36**, 494.

SELECTED ABSTRACTS

Blood group specificity

Chemical basis

MORGAN (1960) discusses the chemical basis of blood-group specificities and points out that a number of the complexities within the ABO and Lewis systems can be attributed to differences in chemical structure. Treatment with liquid phenol, 90 per cent, is required for isolating human blood-group substances. Another procedure is based upon the extraction of dried secretions with dimethylsulphoxide. Blood group substances are readily inactivated by various enzyme preparations. The enzymes may be obtained from fig latex and papaya fruit, from extracts of the livers and digestive organs of snails, and from culture filtrates of *Clostridium welchii* and other micro-organisms. Highly purified specific substances contain 11 or 12 amino acids and 4 sugar components. Threonine, serine and proline constitute about half the total amount of amino acids. The use of quantitative analysis indicates that the specific materials are closely similar in their chemical composition. As compared with A, H or Le^a substances, however, group B substances contain a larger amount of galactose; and as compared with B or H substances, the A substances contain more galactosamine and more total amino sugar. Variations also occur in the glucosamine–galactosamine ratio. Group-specific complexes are mucopolysaccharides, and it is believed that the carbohydrate chains in the materials are tightly integrated with peptide units. One sugar component in each specific substance plays a dominant role in the serological specificity. In A specificity, for example, *N*-acetyl-galactosamine is of primary importance. It is considered that the *A* gene exerts its action in the later stages of the synthesis of the specific mucopolysaccharide and it is probable that gene activity determines the sequence of sugars which constitute the specific determinant structure. With reference to the pathway between gene structure and phenotypic manifestation, experimental evidence indicates that the blood-group gene is responsible only for the final stages of the synthesis of group specific substances. Presumably the last phase is chiefly concerned with the formation of the special carbohydrate structures which in turn determine the serological specificity of the mucopolysaccharide molecule. In collaboration with Watkins, the author has formulated a unifying hypothesis in which it is proposed that a relation exists between the appearance of the ABH and Le^a substances in the secretions and the activity of the independent gene systems L^1 and l^1, S^1 and s^1, and the ABO genes. The scheme for mucopolysaccharide synthesis is based upon immuno-chemical observations in native secretions and isolated blood-group mucopolysaccharides. The genes L^1, S^1, A and B bring about the conversion of a precursor substance into the serologically specific compound which eventually is found in the secretions.

Auto-immune disease

Clonal selection theory

BURNET (1959) points out that the adult animal can differentiate between foreign antigenic substances and native substances which have been present since embryonic and neonatal life. This capacity for recognition is a characteristic function of the mesenchymal cells. According to the clonal selection theory different clones of mesenchymal cells produce specific antibodies. This quality is determined genetically. Immunological experience in the adult is incorporated in clones of cells contained in the spleen, bone marrow, lymphatic glands and various accumulations of lymphoid tissue. An antigen stimulates mesenchymal cells of the appropriate clone to proliferate and to produce antibody. The proliferative stimulus lapses when antigen disappears from the body.

Feldman M., and Yaffe, D. (1959). *J. Nat. Cancer Inst.*, **23**, 109.
Felton, L. D. (1949). *J. Immunol.*, **61**, 107.
Finerty, J. C. (1952). *Physiol. Rev.*, **32**, 277.
Ford, C. E., Ilbery, P. L. T., and Loutit, J. F. (1957). *J. cell. comp. Physiol.*, **50** (Suppl. 1), 109.
— Hamerton, J. L., Barnes, D. W. H., and Loutit, J. F. (1956). *Nature, Lond.*, **177**, 452.
Fourth Tissue Homotransplantation Conference (1960). *Ann. N.Y. Acad. Sci.* In the press.
Gengozian, N. (1959). *J. Immunol.*, **83**, 173.
Gorer, P. A., and Boyse, E. A. (1959). In *Biological Problems of Grafting*. p. 193. Ed. by Albert, F., and Lejeune-Ledant, G. Oxford: Blackwell.
Grabar, P., Courcon, J., Ilbery, P. L. T., Loutit, J. F., and Merrill, J. P. (1957). *C. R. Acad. Sci.*, **245**, 950.
Ilbery, P. L. T., Koller, P. C., and Loutit, J. F. (1958). *J. Nat. Cancer Inst.*, **20**, 1051.
Jacobson, L. O. (1952) *Cancer Res.*, **12**, 315.
La Biologie des Homogreffes. (1958). Paris: Centre National de la Recherche Scientifique.
Landsteiner, K., and Chase, M. W. (1942). *Proc. Soc. exp. Biol., N.Y.*, **49**, 688.
Lennox, B., Dempster, W. J., and Boag, J. W. (1952). *Brit. J. exp. Path.*, **33**, 380.
Lindsley, D. L., Odell, T. T., and Tausche, F. G. (1955). *Proc. Soc. exp. Biol., N.Y.*, **90**, 512.
Lorenz, E., Congdon, C. C., and Uphoff, D. E. (1952) *Radiology*, **58**, 863.
Loutit, J. F. (1960). *Ann. N.Y. Acad. Sci.*, **88**, 122.
Main, J. M., and Prehn, R. T. (1955). *J. Nat. Cancer Inst.*, **15**, 1023.
Makinodan, T. (1957). *J. cell. comp. Physiol.*, **50** (Suppl. 1), 327.
— Gengozian, N., and Shekarchi, C. (1958). *J. Nat. Cancer Inst.*, **20**, 591.
Medawar, P. B. (1945). *J. Anat.*, **79**, 157.
— (1958). *Proc. roy. Soc. B.*, **149**, 143.
— (1959). In *Biological Problems of Grafting*. p. 6. Ed. by Albert, F., and Lejeune-Ledant, G. Oxford: Blackwell.
— (1959b). "Theories of Immunological Tolerance". In *Cellular Aspects of Immunology*, p. 134. Ed. by Wostenholme, G. E. W. and O'Connor, M. London; Churchill (Published 1960).
Mitchison, N. A. (1957). *J. cell. comp. Physiol.*, **50** (Suppl. 1), 247.
— (1959). In *Biological Problems of Grafting*. p. 239. Ed. Albert, F., and Lejeune-Ledant, G. Oxford: Blackwell.
Morgan, W. T. J., and Watkins, W. M. (1959). *Brit. med. Bull.* **15**, 109.
Owen R. D. (1945). *Science*, **102**, 400.
Porter, K. A. (1957). *Brit. J. exp. Path.*, **38**, 401.
— and Couch, N. P. (1959). *Ibid.*, **40**, 52.
Schwartz, R., and Dameshek, W. (1959). *Nature, Lond.*, **183**, 1682.
— Eisner, A., and Dameshek, W. (1959). *J. clin. Invest.*, **38**, 1394.
Simonsen, M., and Jensen, E. (1959). In *Biological Problems of Grafting*. p. 214. Ed. by Albert, F., and Lejeune-Ledant, G. Oxford: Blackwell.
Taliaferro, W. H. (1957). *J. cell comp. Physiol.*, **50** (Suppl. 1), 1.
Third Tissue Homotransplantation Conference (1958). *Ann. N.Y. Acad. Sci.*, **73**, 539.
Thomas, E. D., Ashley, C. A., Lochte, H. L. Jr., Jaretzki, A. III., Sahler, O. D., and Ferrebee, J. W. (1959). *Blood*, **14**, 720.
Trentin, J. J. (1956). *Proc. Soc. exp. Biol. N.Y.*, **93**, 98.
— (1958). *Ann. N.Y. Acad. Sci.*, **73**, 799.
— (1959). In *Biological Problems of Grafting*. p. 207. Ed. by Albert, F., and Lejeune-Ledant, G. Oxford: Blackwell.
Trowell, O. A. (1958). *Int. Rev. Cytol.*, **7**, 235.
Uphoff, D. E. (1957). *J. Nat. Cancer Inst.*, **19**, 123.
— (1958). *Ibid.*, **20**, 625.
— and Law, L. W. (1958). *Ibid.*, **20**, 617.
— (1959). *Ibid.*, **22**, 229.

Induction of tolerance in newborn mice

Phenomenon of runt disease

BILLINGHAM and BRENT (1959) describe the induction of immunological tolerance in newborn mice, and present studies on the phenomenon of runt disease. A major technical problem unsolved by earlier work, was the production of large numbers of tolerant mice for experimental purposes. Injection of homologous tissues into newborn mice, either subcutaneously or intraperitoneally, had produced such a small proportion of tolerant animals as to suggest that at the time of birth most mice had already outlived the "tolerance-responsive" phase of life. Taking a lead from work on newly-hatched chickens, however, the authors have devised a method for the intravenous injection of newborn mice, and the mice so treated with cell suspensions of spleen were found to exhibit tolerance. The method, in some mouse strains at least, was both simpler and more profitable than the inoculation of embryos. The tolerance was often accompanied by the occurrence of a disease, referred to descriptively as "runt disease", which led to the premature death or impaired development of a variable proportion of the subjects, depending upon the particular donor/recipient strain combinations used. The disease was provisionally attributed to an immunological reaction of the inoculated homologous spleen cells against their antigenically foreign hosts. The majority of the mice used in the investigation belonged to laboratory sublines of the following strains: strong A, CBA, AU, C57BL, and C3H. The median survival time of skin homografts transplanted between normal adults of these strains had previously been determined either from biopsy specimens removed at intervals or from the outward appearance of skin homografts on groups of 6–9 animals. Preparations were made of cell suspensions of thymus and bone marrow as well as spleen. The injections were made either through the orbital branch of the anterior facial vein or through the sigmoid sinus. The results of the investigation led to the following conclusions: mice from a wide variety of strains could be made highly tolerant of skin homografts, provided: (*a*) that they were injected with homologous tissue cells immediately or soon after birth, and (*b*) that the tolerance-conferring cells were introduced by a systemic route. In those combinations where chronic sickness or death occurred attributable to reactions of the inoculated cells against their hosts the effect was precluded by the use of bone marrow or immunologically non-reactive cells in place of spleen cells, for example, foetal in place of adult cells or cells from an F_1 hybrid donor, one parent of which was a member of the recipient strain. In the causation of runt disease, although it is probable that the response of the injected cells against the host was a cell-mediated homograft reaction, the possibility that circulating antibodies also played a role could not be excluded. A study of the relationship between tolerance and runt disease showed (1) that there was no reason to regard the state of tolerance as a consequence of the host's lymphoid hypoplasia; and (2) that tolerance aided the homologous cells in so far as it enabled them to persist long enough to do harm; the resemblance between runt disease in tolerant mice and secondary disease in radiation chimaeras was emphasized by the finding that the incidence and severity of secondary disease also appeared to be largely determined by the genetic disparity between donor and host strains. The discovery that a graft may, if it contained sufficient immunologically competent cells, react against the tissues of the host suggests that, at least for some tissues and organs, the clinical homograft problem must now be regarded as composite. The study reveals the danger of attempting to confer tolerance on newborn human infants by the injection of homologous adult leucocytes, a point to be considered when attempting to restore immunologic reactivity in hypogammaglobulinaemic patients. The authors emphasize that lesions produced in the mammalian foetus by maternal isoimmunization need not necessarily by produced by humoral antibodies entering the foetus from the maternal circulation.

Primary and secondary immune responses

Effect of 6-mercaptopurine

SCHWARTZ, EISNER and DAMESHEK (1959) record experiments in which rabbits were given an intravenous injection of 10–15 microcuries of radio-iodinated human serum

In the foetus, however, the antigenic determinants hereditarily acquired cause suppression or death of those immature clones which could specifically react with them. These are the "forbidden clones". Homeostatic control of the structure and function of the body thus includes the mechanism by which a "forbidden" clone is eliminated. With regard to cells of mesenchymal origin the main function of the lymphocyte is to carry immunological information. The macrophage takes up antigen but does not give rise to antibody, on the other hand, the production of antibody is a characteristic function of the plasma cell. Contact of an antigenic determinant with the lymphocytes may result in the formation of plasma cells and of similar cells of the lymphoid series. It is believed that somatic cells mutate with the same order of frequency as germ cells. The factors required for the periodic production of forbidden clones include primary mutation, an accessible source of antigenic determinant and an adequate supply of mesenchymal cells with conditions appropriate for conversion to plasma cells. In the case of disseminated lupus erythematosus (DLE) forbidden clones proliferate and the pathogenic action is directed against antigenic determinants which are liberated after the tissues have reacted to immunological damage. The symptomatology of the disease is characteristically multiple, a feature which may be correlated with the presence of numerous antigenic determinants. Furthermore, auto-immune diseases such as DLE, rheumatoid arthritis and periarteritis nodosa are closely interrelated. The serum in DLE contains reactive globulins which correspond to antigenic determinants in the nuclei of mesenchymal cells. A minor damaging process such as serum sickness may provide a focus for pathological forbidden clones. In the development of clones the antigenic determinant *X* must be of relatively limited accessibility. Thus in chronic acquired haemolytic anaemia the antigens are not those of the ABO system or of any other system which can be determined easily. Significance is attached to the fact that splenectomy is often successful in curing or alleviating the symptoms of acquired haemolytic anaemia. It is implied that antigen accumulates in the spleen from ingested erythrocytes and that forbidden clones are inhibited against common antigens. The antigenic determinant *X* in the spleen acts as a proliferative stimulus. In addition, the spleen is a rich source of lymphoid cells and supplies a suitable environment for the development of plasma cells.

Skin transplantation immunity

Hypersensitivity reactions of the delayed type

According to BRENT, BROWN and MEDAWAR (1959) it is unlikely that all homografts of all tissues are destroyed by similar mechanisms. Destruction of orthotopic skin homografts may be brought about either by the action of serum antibodies or by the topical effect of activated lymphoid cells. Various investigators have adduced evidence in favour of the humoral hypothesis. For example, it is known that homografts of normal tissues may cause the formation of haemagglutinins, haemolysins and other serum antibodies. Antigens associated with the formation of these antibodies are of wide distribution in the fixed tissues and have a common genetic determination with antigens which produce transplantation immunity. On the other hand, in animals transplantation immunity can be transferred by means of activated lymphoid cells but not by immune serum. In guinea-pigs the homograft reaction can be elicited as a cutaneous hypersensitivity of the delayed type. If an impure antigen can elicit transplantation immunity it can also give rise to a tuberculin-like reaction when it is injected intramuscularly into animals sensitized by skin homografts. This direct reaction has a latent period of 4–8 hours and is maximal in 24–36 hours. Its intensity varies with the degree of sensitivity of the recipient and the dosage of antigen. The reaction can be transferred through animals by means of activated lymphoid cells. As compared with the direct reaction, the transferred reaction takes longer to reach its peak and declines more slowly. Transfer reactions are not produced when demonstrably activated lymphoid cells, heated to a temperature of 48 5°C. or dried in the frozen state, are injected into isologous recipients. Structural rather than soluble antibodies may be responsible for mediating the cellular immunity. Alternatively, an orthodox soluble antibody may be produced in such small quantities that its effects can be discernible only in the neighbourhood of the activating cells.

character of chromosome-breakage suggests that all cells exhibiting the same set of chromosomal rearrangements are related by mitotic descent from a single ancestral cell changed by irradiation. They therefore constitute a clone of cells *in vivo*. In these changes the chromosome number remains 40. Clones in "spontaneous reversion" were first identified in a CBA mouse irradiated at 850 roentgen and injected with rat bone marrow. A clone, with one exceptionally long and one exceptionally short chromosome, was present in bone marrow, spleen and the two inguinal lymph nodes, comprising 32 per cent of the dividing cells in the latter organs. On the other hand radiation-chimaeras may be very stable in that donor-type tissue persists and spontaneous reversion does not occur. These homologous chimaeras were produced by irradiation of CBA mice with 950 roentgen of x-rays, followed by intravenous injection of (CBAxT6) F_1 bone marrow. After a fortnight, they were injected intravenously with (*a*) saline solution—mock treatment; (*b*) suspension of normal spleen-cells; and (*c*) suspension of sensitized spleen-cells. In series (*a*) the mitotic cells in bone marrow, spleen and thymus were almost uniformly those of the original donor-type containing the T6 chromosome. Series (*b*) and (*c*) did not differ appreciably up to the tenth day, but (*c*) was incomplete owing to the death of two animals. A second experiment was therefore carried out. In series (*b*), given normal spleen-cells, transpopulation was induced by three weeks, in one animal in all three tissues, in another, only the spleen. By six weeks, transpopulation was confirmed. The pattern was similar in series (*c*) given sensitized cells. In a further experiment suspensions of lymph node instead of spleen-cells were injected. Transpopulation was not induced. It is concluded that both spontaneous reversion and induced transpopulation are due to the superior physiological competence of the finally predominating cell-line, rather than ascendency through a reaction of immunity.

Transplanted reticulo-endothelial cells in mice

Reactions

Gorer and Boyse (1959) comment upon the susceptibility of leukaemic cells to direct attack by antibody. In confirmation of the findings of Amos and Wakefield, it is pointed out that the cells may be destroyed in Algire-type diffusion chambers in immunized homologous hosts. Normal cells from the spleen and lymphatic glands react like longer-established leukaemias. Bone-marrow suspensions are usually less susceptible. Thymus samples, including samples with foci of leukaemia, may be highly sensitive to the cytotoxic action of guinea-pig serum, but the reactions of thymus tissues to antibody are variable. Splenic cells from a parent of an F_1 mouse immunized against the other parent may either die in F_1 hosts or proliferate and kill the hosts. In the latter event the spleen and lymphatic glands are invaded and the resident cells are destroyed. Replacement of erythropoietic tissue is a relatively slow process. So far as homologous disease is concerned, the lymphoid cells of the donor and host are destroyed. Allergic death of the donor cells may be attributed to union of host antigen with antibody attached to the donor cells. In fatally irradiated mice prior treatment with antibody may prevent the protective effect of homologous bone marrow and spleen. Neither auto-antibodies nor organic specific antibodies are implicated. The investigators carried out experiments upon two groups of mice which had been exposed to lethal whole-body irradiation. The animals were given intravenous injections of homologous marrow or spleen. One group received a small amount of immune serum directed against the homologous cells. Either saline or normal mouse serum was administered to the control group. Whereas the protection of the control group was found to be adequate, the experimental animals died like irradiated unprotected mice.

Immunogenetic studies

X-irradiated mice treated with haematopoietic cells and grafted with tumour tissues

Immunogenetic studies on x-irradiated mice treated with haematopoietic cells and grafted with tumour tissues are presented by Feldman and Yaffe (1959). It was found that inoculation of x-irradiated animals with spleen or bone marrow cells from homologous donors gave rise to colonization of the haematopoietic tissues of the irradiated

albumin (HSA-1) mixed with 20 milligrams of "carrier" human serum albumin (HSA). A specimen of blood was obtained from the marginal ear veins 15 minutes after the injection and the specimen was used as a standard for comparison with other blood samples taken at intervals during the course of the experiment. The rate of disappearance of antigen was determined by means of the isotope technique employed by Talmage and his colleagues, and the appearance of antibody was measured by the ammonium sulphate fractionation method. It was found that HSA-1 disappeared from the serum in three phases. About two-thirds of the radioactivity disappeared within the first 24 hours. The remaining radioactivity then showed a logarithmic decay curve which was similar to the curve obtained with other circulating proteins. An accelerated disappearance phase was initiated on the seventh day. At the same time, there was an increase in the amount of HSA-1 bound to globulin, a finding which denoted the appearance of circulating antigen-antibody complexes. By the ninth day most of the detectable isotope was in the globulin fraction. On the twelfth day tannic acid haemagglutination tests proved to be positive for the presence of "free" humoral antibody. The antibody titres were highest on the eighteenth day and then began to decline. These primary immune responses were completely blocked when 6-mercaptopurine (6-MP) in a dosage of 6 milligrams per kilogram was administered daily by the intramuscular route. Smaller doses of 6-MP showed a linear relationship to the effect upon the primary response. During the course of another series of experiments the animals were given a single intravenous injection of HSA, 100 milligrams. "Carrier" protein, 20 milligrams, and HSA-1, 10-15 microcuries, were injected intravenously 6-8 weeks later. Immune responses were detected at a relatively early stage. A dose of 6-MP which had completely blocked the onset of the primary response was found to be only partially effective in blocking the secondary type of response.

Drug-induced immunological tolerance

SCHWARTZ and DAMESHEK (1959) describe experiments in which the use of 6-mercaptopurine led to the apparent induction of immunological tolerance. Adult rabbits were given an intravenous injection of human serum albumin which was labelled with iodine 131. Subsequently intramuscular injections of 6-mercaptopurine were administered daily for two weeks. In a control group only the labelled antigen was injected. An immune-disappearance phase developed in this group but not in the animals treated with 6-mercaptopurine. The latter group showed an exponential disappearance of antigen. The mode of disappearance was similar to that seen after injection of homologous albumin and failure to form antibody was inferred. About a month after the first injection both groups of animals received intravenously a second injection of the albumin antigen together with bovine *gamma*-globulin. A typical secondary response to human serum albumin was recorded among the controls and precipitating antibodies to the injected albumin appeared in the serum. The drug-treated group still showed no reaction to the albumin but did react to bovine *gamma*-globulin, indicating the specific nature of the change in immunological reactivity. Among the drug-treated animals there was no evidence of the formation of anti-human serum albumin. The authors suggest that an information-storing device is established by the metabolic activity which antigen provokes in antibody-forming cells. Among animals treated with 6-mercaptopurine there is gross dysfunction of the storing device. The term, acquired immunological tolerance, is applicable to drug-induced tolerance and to the response of the immature animal.

Spontaneous and induced changes in cell populations

Heavily irradiated mice

BARNES and his colleagues (1959) discussed spontaneous and induced changes in cell populations of heavily irradiated mice, whose recovery has been affected by the intravenous injection of normal haemopoietic cells. The recovered animal is a chimaera containing populations of cells derived from the original host and the donated material. After a variable period, in some combinations of host and donor, native cells reappear and wholly or partially replace the donor cells, a condition of "spontaneous reversion". The cells of these reverted tissues may contain chromosome-translocations. The random

were found to be highly susceptible to transplantation immunity. The low antigenicity of the tumour cells, therefore, was not caused by the loss of the H antigens, but was attributed to a low rate of antigen emission. An analysis of these properties revealed indications that the change of SBLI to SBLx involved a genetic transformation produced by the conditions prevailing in radiation chimaeras; the acquired homotransplantability was found to be reversible; the result of transplantation of SBLx tumours back into C57BL or into (C3H × C57BL)F_1 mice was a complete loss of homotransplantability; the mere existence of the isologous C57BL antigens in the host was sufficient to give rise to this reversed change and therefore the SBLxBL tumours formed in this way regained the original antigenicity of SBLI; the reversal occurred only if the SBLx tumour was transplanted to hosts of foreign strains following 9–16 days of growth in C57BL mice; prolonged growth of the tumour in C57BL mice did not produce a loss of strain specificity. The observation that there is a crucial period in which homotransplantability is lost suggests the possibility of a host's reaction in the reversal change, and the fact that this occurs after 9–16 days of growth suggests that this response is similar to that of the homograft reaction.

Irradiation protection by bone marrow

Evaluation of genetic factors

Uphoff and Law (1959) state that mice may survive the lethal effect of x-rays if an intravenous injection of splenic cells or bone marrow is administered subsequent to irradiation. When homologous or heterologous marrow is injected recovery is only temporary, and it is likely that death results from a homograft reaction against the irradiated host. In certain F_1 hybrids inoculation of hybrid marrow affords better protection than marrow derived from parental strains. This effect is more defined when the parental strains are of different genotypes at the H-2 locus. The authors carried out experiments in which mice aged 3–4 months were irradiated with doses of 700–800 roentgens. After irradiation the animals received injections of either isologous or co-isologous marrow. With isologous marrow both protection and long-term survival were good, but with co-isologous marrow the animals suffered from severe diarrhoea, dermatitis and extreme emaciation. Apparently a single gene difference at the H-2 locus had resulted in a severe reaction during the secondary phase of recovery. On the other hand, no reaction was produced by difference at the H-3 locus and the response at the H-1 locus was variable. When the strains were of different H-2 phenotypes no combination of inbred-strains gave good long-term survival. Nine combinations in which the donor and recipient were of the same H-2 phenotype did result in long-term survival. Among hybrids of the genotype H-2^d H-2^k bone marrow from strain A induced a secondary response that was attributed to an immune response of the graft against the host. A variable response was observed in F_1 hybrids which were treated with parental-strain marrow. The variability was ascribed to the different thresholds of response to foreign antigens when present only in single dose.

Transplantation of homologous bone marrow and skin

Experiments in rabbits following total-body irradiation

Wilson and his colleagues (1959) describe experiments in which rabbits were submitted to total irradiation of the body. Subsequently the animals received transplants of homologous bone marrow and skin. White male New Zealand rabbits, genetically unrelated, were given a total of 1,100 roentgens. In addition, daily injections of penicillin and streptomycin were administered. Female weanling rabbits were killed and the ears were shaved, removed, soaked in isopropyl alcohol, 50 per cent, and rinsed in saline solution. Five full-thickness rectangles of skin were dissected from the dorsal surface of each ear and wrapped in sterile saline sponge. Marrow was curetted from the main long bones of the carcass and placed in Hank's balanced salt solution. After being passed through metal screens, a marrow suspension was prepared and injected into the lateral ear vein

recipient by the genetically "foreign" cells. If, therefore, homologous donor cells repopulate the antibody-forming organs of the irradiated animal then theoretically the antibody-forming cells of the "homologous radiation chimaera" can be stimulated immunologically by the isoantigens of the host. The resultant transplantation immunity against the host's tissues was postulated to be the main factor in the lethal "secondary disease" of homologous chimaeras. In the present investigation the mice used were of the inbred strain C3H and C57BL and C57BL/6: all were 90–100 days old. The mice were irradiated in Lucite containers with a target object distance of 50 centimetres; the mice were exposed to 800 roentgens (12 days LD_{100}) of x-rays (200 kilovolts, 15 milliamperes, filtered with Al 1 millimetre and Cu 0·5 millimetre) delivered at a dose rate of 30 roentgens per minute. Approximately 18–19 hours after irradiation the animals received intravenous injections of either infant spleen cells or embryonic liver cells. The tumours used in the transplantation experiments comprised: the ascites form of Sarcoma MCIM; Sarcoma CIO, produced in C3H mice by subcutaneous administration of benzopyrene; and Sarcoma SBLI, similarly produced in C57BL mice. Sarcoma CIO and Sarcoma SBLI are strain-specific tumours; Sarcoma MCIM is a semi-homotransplantable tumour that gives successful homografts after intraperitoneal but not subcutaneous or intramuscular injection to mice of foreign strains. The results of the investigation demonstrated regression of homografts of Sarcoma CIO and Sarcoma MCIM (of C3H origin) in irradiated C57BL animals treated with C57BL infant spleen, and their progressive growth in irradiated animals treated with C57BL foetal haematopoietic cells. This finding indicated the ability of immunologically competent donor cells to form transplantation mmunity against foreign antigens, and in this way substantiated the graft versus host theory as the basis of "homologous secondary disease". The study revealed that tumour grafts produced metastases in irradiated animals, and showed that their development was influenced by irradiation and immunogenetic factors. Transplantation of Sarcoma SBLI into a variety of types of genetic chimaeras was accompanied by immunogenetic changes in the tumours, which were indicated by the loss of strain specificity; this change was found to be determined mainly by the effect of total-body irradiation of the host and the absence of isologous C57BL cells. Analysis gave definite indications that the acquired homotransplantability of SBLx sublines results, basically, from immunogenetic transformation induced by the host, and is not a result of selection of pre-existing compatible cell variants. The study also showed that cortisone, like total-body x-irradiation, elicited he progressive growth of pre-existing metastatic emboli: it seems that these factors may have a similar effect on the resistance capacity of the lymphatic system to tumour metastases.

Changes induced in tumours grown in radiation chimaeras

Immunogenetic changes induced in tumours grown in radiation chimaeras have been investigated by Yaffe and Feldman (1959). The results of a previous study showed that tumours grafted on x-irradiated mice that had been treated by foetal haematopoietic cells may undergo immunogenetic changes manifested in an acquired homotransplantability of the original strain-specific tumour. In the present study an analysis has been made of the immunogenetic properties of tumours that have acquired homotransplantability in these conditions. The C3H and C57BL strains of mice used were obtained from the same source as those used previously. The tumours comprised: Sarcoma SBLI, produced in C57BL mice; SBLx25 and SBLxI, two sublines of Sarcoma SBLI; the ascites form of 6C3HED lymphoma, produced in C3H mice; the 6C3HED-ICR subline; and the ascites form of MCIM and MCIA Sarcomas, both of which are of C3H origin. C3H anti-C57BL serum was prepared by inoculating C3H mice with cell aggregates of minced C57BL liver and spleen suspended in physiological saline solution; absorptions of antiserum by tumour cells were made by incubating antiserums diluted 1x4 in saline with equal volumes of minced tumour tissue; each sample of antiserum was absorbed twice for one hour at 37°C. The results of the study showed that the SBLx tumours had lost their original antigenicity of SBLI, and that the homotransplantability of SBLx was therefore based on its inability to elicit an immune response, although SBLx tumours

Morgan, W. T. J. (1960). *Proc. roy. Soc., B.*, **151**, 308.
Schwartz, R., and Dameshek, W. (1959). *Nature, Lond.*, **183**, 1682.
— Eisner, Anna, and Dameshek, W. (1959). *J. clin. Invest.*, **38**, 1394.
Stark, R. B. and Dwyer, E. (1959). *Surgery*, **46**, 297.
Uphoff, D. E., and Law, L. W. (1959). *J. Nat. Cancer Inst.*, **22**, 229.
Yaffe, D., and Feldman, M. (1959). *J. Nat. Cancer Inst.*, **23**, 133.
Wilson, R. E., Dealy, J. B. Jnr., Sadowsky, N. L., Corson, J. M., and Murray, J. E. (1959). *Surgery*, **46**, 261.

of each recipient animal. Then the animals were anaesthetized and the ears were prepared to receive the grafts. Both an autograft and a skin graft from the bone-marrow donor were placed on the ear of the recipient. Control rabbits received similar treatment with the exception of bone-marrow injections. A higher survival rate was recorded in rabbits which received marrow from a single donor than in rabbits which were given pooled marrow. In both types of marrow treatment, however, the improvement was significantly greater than the improvement observed in the controls. All animals which accepted homologous bone marrow also accepted skin. On the other hand, animals which failed to accept pooled bone marrow eventually rejected the skin homografts. With regard to the clinical application of these findings, the authors believe that marrow transplants and skin homografts can be achieved, especially in single-marrow recipients. Marrow-pooling techniques may be used for securing an adequate supply of viable cells. Undue delay in identifying the most suitable donors of other organs or tissues would be obviated by the prompt rejection of skin grafts from donors whose marrow had been rejected. Thus the critical organ or tissue could be grafted at an early stage in the post-irradiation period and presensitization of the recipient by intended donors would be prevented.

Skin homografts in rabbits

Enhancement using elements of homologous whole blood

STARK and DWYER (1959) describe experiments which were performed in order to establish the relation between the elements of the blood and the survival of homografts. Skin homografts, 2·5 centimetres in diameter, were transplanted to the ears of rabbits. Five days after the transplantation local necrosis developed in at least 50 per cent of cases. At this stage biopsy revealed maximal necrosis accompanied by an infiltration of mononuclear cells. A second homograft was transplanted on the fifth day. The same donors and hosts were selected, but the transplant was attached to the opposite ear of the host. Within two days the second-set homografts had become totally necrotic without any evidence of mononuclear-cell infiltration. The experiments were repeated after injecting the host with homologous whole blood which had been obtained by puncturing the donor's heart. It was found that preliminary treatment with whole blood had prolonged the viability of the homografts. Isohaemagglutinins were not detected in the host. During the course of further experiments it was ascertained that enhancement was due to the injection of erythrocytes and that the red-cell haemolysate constituted the enhancing agent. On the other hand, daily injections of a series of haemolysates failed to produce enhancement. After the injection of erythrocytes tagged with radioactive chromium the lymphatic glands showed traces of radioactivity. Greater prolongation of the life of the transplant was observed after excision of the auricular lymphatic gland and transplantation of the skin homograft to a distal part of the ear. The authors associate the regional lymphatic glands with the mechanism of rejection of the homograft and point out that the enhancing agent causes paralysis of the immune response, a phenomenon which is termed immunoparalysis by Felton.

REFERENCES

Barnes, D. W. H., Ford, C. E., Gray, S. M., and Loutit, J. F. (1959). "Progress in Nuclear Energy, Series VI." In *Biological Sciences*. Vol. 2, p. 1. London; Pergamon Press.

Billingham, R. E., and Brent, J. (1959). *Phil. Trans. B.*, **242**, 439.

Brent, L., Brown, J. B., and Medawar, P. B. (1959). *Biological Problems of Grafting*. p. 64. Oxford: Blackwell.

Burnet, F. M. (1959). *Brit. med. J.*, **2**, 465, 720.

Feldman, M., and Yaffe, D. (1959). *J. Nat. Cancer Inst.*, **23**, 109.

Gorer, P. A., and Boyse, E. A. (1959). *Biological Problems of Grafting*. p. 193. Oxford: Blackwell.

require special techniques which are already well defined and are within the range of a general surgeon.

The technique of transplanting tissues has advanced at a greater pace than the techniques for collection and preservation of tissue on the one hand and our understanding of the mechanism of biological rejection on the other. Biological rejection amounts to this: unless two individuals of the same species are genetically identical they cannot permanently exchange tissues. This is a depressing situation because there is a constant clinical demand for biological spare parts which cannot possibly be met at the moment because of this strict zoological law. Our frustration does not end here for there is yet another reason for pursuing the homograft problem: we are, ourselves, in a sense, homografts. The maternal circulation is separated from the foetal and one writer has argued ". . . that there is only one singly sufficient reason, an immunological reason, why its isolation should be so strict" (Medawar, 1958a). More has still to be learned about the so-called placental barrier before we can agree wholeheartedly with this writer on the strict separation of the two systems. We do know that if antigens pass from the foetus into the maternal circulation antibodies can develop which, when they pass into the foetal circulation, can cause harmful effects. It may be that many cases of unexplained stillbirths are due to such reactions. Congenital bleeding of the newborn results from the leakage of foetal red cells bearing the D antigen (other antigens have been reported but are less important) into the maternal circulation. The maternal tissues produce an anti-D antibody (that is the Rh antibody) which finds its way across the placenta into the foetal circulation and on to the red cells causing haemolysis. This, then, is a form of homograft reaction. The Rh antibody is not a naturally occurring antibody like the ABO and other blood group system antibodies but is actively acquired. So far as we know there are no naturally occurring anti-homotissue antibodies; if and when such antibodies appear they are actively acquired as the result of a specific challenge of antigen.

THE GENETIC LAWS OF TRANSPLANTATION

Tissue can be successfully and permanently exchanged between uniovular twins. This suggests that there is a fundamental genetic control of tissue exchanged between two people of the same species. It is generally agreed that where genetic identity between donor and recipient does not exist, a homograft will be rejected by the host by means of an antigen-antibody reaction (Medawar, 1958a, b). It would appear, therefore, that the homograft problem has been traced to a no-man's land where genetics and immunology meet.

Tissue can be exchanged between members of an inbred strain of mice and rats. Inbreeding leads to genetic uniformity by progressively increasing the proportion of homozygous gene pairs present. There is no real genetic test for genetic uniformity but skin grafting between members can establish very accurately whether or not there is absolute genetic uniformity. A survey has been published of some of the inbred strains of laboratory animals that can be used in homografting work (Billingham and Silvers, 1959a). The statement that tissue can be permanently exchanged between members of an inbred strain is not entirely true. In certain

TISSUE TRANSPLANTATION

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Tissue transplantation and cognate problems have greatly extended their frontiers into medicine and biology in the last decade. It would appear that the rejection of a homograft, auto-immune disease, Rh immunization, runt disease and the evolution of the reticulo-endothelial system all have something in common. This being so, this article will attempt to review briefly the general nature of the homograft problem, then try to relate it to the various so-called auto-immune diseases and finally, will briefly review the present knowledge relating to the homotransplantation of skin, organs and bone marrow.

INTRODUCTION

There are three main problems involved in the transplantation of tissues. These are: the supply, the application and the successful incorporation of the transplanted tissue. The supply of tissues for transplantation can be either from a person's own body (as, for example, skin and bone grafts, or ileum to replace bladder, colon to replace oesophagus, or jejunum to replace stomach) or from another person's body (such as cornea, blood, blood vessels, kidney, bone and bone marrow). Tissue taken from one area and placed in another area of the same person is termed an autograft. If a spare part is supplied by another person of the same species it is referred to as a homograft. The former is usually successful and when it fails there is invariably some technical rather than biological reason for its failure. A homograft, on the other hand, is usually not permanently successful and the reason for its failure is biological incompatibility which requires some time to manifest itself.

The importance of pursuing the problems of tissue transplantation lies in the gravity of the occasion on which such grafts are urgently required rather than in any wide clinical application. The number of occasions on which organ transplantation, for example, could be carried out will be determined by the supply. The source will seldom be the cadaver so far as organs like kidneys are concerned because they have been found unsatisfactory (Hume, Merrill and Miller, 1955). It is possible that other organs will be salvaged successfully from cadavers provided suitable means of preserving them can be found.

The supply of tissues suitable for transplantation constitutes a greater problem than the technique involved in transferring them. Skin grafting is a skilled procedure which is now routine everywhere. Organs such as kidney, heart and lungs

homotransplants are concerned, there would not appear to be any obvious histological signs of an antigen-antibody reaction at the moment when they suddenly stop functioning. It has been suggested that since free circulating antibodies have not been clearly demonstrated in the serum of a sensitized animal, the destructive antibodies may be contained in their lymphocytes; the so-called endo-antibodies (Medawar, 1958b).

Homograft rejection and delayed hypersensitivity

The difficulty in detecting free circulating antibodies in the serum of animals that have rejected a homograft and the inability to transfer passive immunity by serum infusions led some authors to postulate that the homograft rejection phenomenon involved a process akin to tuberculin hypersensitivity. A certain amount of evidence has since been accumulated in favour of this concept. It is as follows.

(1) It has been shown by several workers that passive immunity to homografted tissue could be transferred by a suspension of cells from already sensitized animals, that is, animals which have already rejected a homograft (Medawar, 1958b). In this respect, an exact parallel could be drawn between the homograft rejection process and tuberculin hypersensitivity.

As a corollary to this fact came the report that if host cells could be prevented from making contact with homografts of tumours, by inserting them in diffusion chambers designed to allow plasma but not cells to flow inside, no rejection took place (Prehn, Weaver and Algire, 1956). Unfortunately, for the present and other arguments this report has not been confirmed for normal tissues (Egdahl, Roller and Varco, 1957; Jordan, Foster and Gyorkey, 1958). In addition, the technical difficulties are so great that it is doubtful whether the diffusion chamber technique is a reliable tool for establishing the required data.

(2) The inability to detect free circulating antibodies and the inability passively to transfer immunity by serum were facts common to both processes.

(3) The specificity involved has been found to be specific only for the original sensitizing donor cells or tubercle bacilli.

(4) The reaction against skin homografts in guinea-pigs can be made to express itself as a hypersensitivity reaction of the delayed type.

So far, so good. However, there is a fundamental difference in their reactions to total-body irradiation. Once an animal has become sensitized to a homograft, no amount of irradiation will break down that immunity. Once an animal has responded with a typical hypersensitivity reaction, total-body irradiation can break it down (Lennox, Dempster and Boag, 1952). So far as we know at the moment this is unique, because immunity to bacteria other than the tubercle bacillus is not broken down by irradiation. It is for this reason that total-body irradiation must be given prior to the challenge with antigen otherwise a normal antibody titre will develop. In view of this profound difference in response to x-irradiation, it would not be wise to push the similarity of tuberculin hypersensitivity and homograft rejection too far. A detailed discussion is available in a recent review (Lawrence, 1959).

inbred strains the females, while permanently accepting homografts from other females, will not permanently accept skin homografts from the males (Eichwald and Silmser, 1955). Skin and kidneys can be permanently exchanged between identical or monozygotic human twins (Murray, Merrill and Harrison, 1958). Skin grafting has been used to establish the identity of twins in a group of children (McIndoe and Franceschetti, 1950). Skin (Billingham and his colleagues, 1952) and kidney (Gammeltoft, Neimann Sorensen and Simonsen, 1955) can be exchanged between dizygotic twins in cattle. This latter dispensation is explained on the basis of the synchorial nature of the circulations *in utero*; twin cattle are born with a mixture of one another's blood, that is, they are blood chimaeras (Owen, 1954). This situation of tolerance to each other's tissue does not obtain in the case of twin lambs (Lampkin, 1953).

THE IMMUNOLOGICAL BASIS OF THE TRANSPLANTATION REJECTION PROCESS

The evidence for what has come to be known as the immunological basis of homograft rejection is as follows: skin grafted between two members of the same species survives several days (in man the survival time may be some weeks) and then undergoes liquefaction and sloughs off. If, after an interval of a few days, a second skin graft from the same donor to the same recipient is applied, it will slough more quickly than the first graft. If the second skin graft were to come from another donor it would survive roughly for the same time as the first skin graft (Medawar, 1944). The natural histories of the first and second challenge of tissue could not be more different. The second reaction is not an augmented edition of the first—it is quite different. From these experiments it has been concluded that the skin graft has evoked an actively acquired immunity in the host, that it is gene-transmitted and that it is individually specific.

One's first reaction to this statement is concern about detectable antibodies in the serum of animals which have rejected homografts. Furthermore, one would want to know whether or not one can passively immunize a non-sensitized animal with the serum from an animal that had rejected a homograft. The evidence so far is very disappointing in respect of both the detection of circulating antibodies and the transfer of passive immunity by serum. Passive immunity can, however, be transferred by sensitized cells (Medawar, 1958b).

A number of reports in the literature indicate that in certain circumstances antibody-like substances can be detected (Amos and his colleagues, 1954; Bollag, 1956; Mitchison and Dube, 1955; Woodruff and Forman, 1950). Antibodies to tumours can quite frequently be demonstrated in the mouse (Gorer, 1956). One author failed to detect antibodies to kidney homotransplants (Simonsen, 1953). Unfortunately, there is no obvious correlation between the rejection of homograft and the peak of antibody formation against either tumour grafts or grafts of normal tissues (Hildeman and Medawar, 1959). Furthermore, homografts of skin can be rejected by foetal lambs at a stage of development prior to their acquiring the ability to produce *gamma*-globulin (Schinkel and Ferguson, 1953). This is a crucial piece of evidence and urgently requires confirmation. So far as kidney

periods (Main and Prehn, 1955). A similar procedure has permitted a homotransplanted kidney to survive normally for 49 days before the dog died of an infection (Mannick and his colleagues, 1959). This is the first report of a successful bone marrow and kidney homotransplant in the dog, which is a particularly resistant animal so that successful grafting with bone marrow is rare. Species differences in resistance to total-body irradiation make an overall assessment of this approach rather difficult.

Steroids

As in so many other fields of biology, steroids were introduced into homografting experiments with a great deal of éclat and with great expectations. Chaotic, to say the least, were the results. They were so disappointing that, after sober reflection, this method of conditioning the host has been largely abandoned. Cortisone, as reported by one group of writers, can prolong the survival of skin homografts if applied locally (Billingham, Krohn and Medawar, 1951). This experiment was performed in the rabbit and requires confirmation. Massive doses, 200 milligrams per day to 22-kilogram dogs, failed to prolong the survival of kidney homotransplants which actually excrete the steroid (Dempster, 1953c). Cortisone given in this way can, however, virtually suppress the development of plasma cells in homotransplanted kidneys and can maintain a reasonably good blood supply during the phase when such kidneys suddenly cease functioning.

Enhancement: active immunization or desensitization?

A preliminary course of injections of freeze-dried tissue is given to an animal. The tissue, usually tumour tissue, in this state is capable of evoking an antibody response (Kaliss, 1957, 1958). There appears to be a causal connexion between the circulating isoantibodies and the prolonged survival of the graft which does occur. Skin homografts have survived longer than usual in rabbits which have had preliminary intravenous injections of dissociated epidermal cells (Billingham and Sparrow, 1955). Other efforts to effect enhancement for normal tissue homografts have failed. The course of preliminary injections must be given intravenously so far as normal skin homografts are concerned. If the injections are given by any other route immunity is induced and not its opposite, enhancement. There seems to be no clinical application of this seemingly bizarre method. On close inspection the published results are not impressive.

Actively acquired tolerance

The theoretical background to this approach is as follows: dizygotic twin cattle are blood chimaeras, that is, they contain a mixture of each other's red blood cells (Owen, 1945). The circulations of these animals are confluent *in utero*. Tissue can be successfully exchanged between such twins and this is thought to be due to the exchange of antigens at an early foetal stage (Billingham and his colleagues, 1952). It was then shown that a challenge of antigen at an early foetal stage rendered that animal tolerant to the same antigen when it became adult (Felton, 1949; Simonsen, 1957). Then it was shown that a foetus injected with suspensions of living cells will, when adult, accept skin homografts from the donor of the cells (Billingham, Brent and Medawar, 1953). This result was associated with a

Tumour transplantation

It is widely believed that the genetic laws of homotransplantation apply to grafts of neoplasms and normal tissues alike.

There are difficulties in accepting this without reservation. There are homotransplantable tumours—not many—but some. The reason for transmissibility in certain instances may be that a virus is the causative agent and hence no immunological or genetical explanation is required. But, some solid tumours are transmissible between two strains and here they part company from the strict laws of transmissibility obtaining in normal tissue (Dunham and Stewart, 1952). For this reason one must regard the statement that neoplastic and normal tissues are under the control of the same genetic laws of transplantability with great reserve. So common is the detection of serum antibodies to tumours in the mouse, that one author regards the appearance of these antibodies as having some functional relationship to the regression of tumour grafts (Gorer, 1956); this attitude would appear to be proved in recent work (Gorer and Boyse, 1959). However, at the moment there would not seem to be any obvious correlation between the two. These unhappy data have undermined our confidence in free circulating antibodies being concerned in auto-immune disease; in these also there would appear to be no correlation between the severity of the disease and the titre of serum antibody. The present evidence for the same zoological laws operating for normal and neoplastic tissues is so weak that an uncommitted attitude to this aspect of the problem appears to be wise until more facts are available.

MODIFICATIONS OF THE HOMOTRANSPLANT REJECTION PHENOMENON

On the basis that an antigen-antibody reaction is involved in the rejection of homografts many efforts have been made to abrogate this reaction. Most have been signal failures. In some instances, Nature herself has prepared suitable preparations for study—the agammaglobulinaemics. Abrogation of the rejection phenomenon has been sought either by conditioning the host or by conditioning the donor tissue, or both. Conditioning the graft has had a short history and attempts to bring this about have been reviewed elsewhere (Dempster, 1951). We will now discuss some of the attempts to modify the host.

Total-body irradiation

The aim of total-body irradiation is to destroy the reticulo-endothelial system of the future host. Sublethal doses can inhibit the development of an antibody titre to bacterial antigen for about 30 days (Craddock and Lawrence, 1948), but thereafter the titre rises to normal levels. Sublethal doses can prolong the survival of skin homografts in rabbits (Dempster, Lennox and Boag, 1950) and mice (Hardin and Werder, 1954). This effect would suggest that skin homografts succumb to an antibody reaction from the host. A further refinement of the irradiation technique is to administer lethal doses of x-rays followed up a few days later with a homograft of bone marrow. When the animal is well recovered skin homografts are applied and, in certain instances, can be successful for considerable

Homohaemotherapy

By injecting donor's blood intramuscularly into homografted mice a prolongation of the skin grafts was effected (Marino and Benaim, 1958). This technique is not consistent in its results but technical errors may explain the failures.

Nitrogen mustards

An animal can still reject a homotransplanted kidney within the normal limits even when splenectomized and subjected to large doses of cortisone and nitrogen mustards (Baker and his colleagues, 1952). This indicates that either an antigen-antibody reaction is not involved in the homograft rejection or that the rejection can occur with extremely small levels of antibody. Prolonged survival of skin homografts have been reported in rats pretreated with nitrogen mustards (Levinson and Necheles, 1956).

Streptokinase-streptodornase

Skin homografts can be made to survive longer by the action of streptokinase-streptodornase (Dukes and Blocker, 1952).

6-mercaptopurine

A kidney homotransplanted to a dog treated with 6-mercaptopurine has survived 47 days (Calne, 1960).

Disease states

Certain disease states are associated with defects in the immunological system. These are as follows.

Hodgkin's disease

It has been shown that a large percentage of patients with Hodgkin's disease are unresponsive to skin tests (Schier and his colleagues, 1956). Since there is some evidence to suggest that homograft rejection and delayed hypersensitivity have something in common, it was decided to carry out skin homografting on these patients (Kelly, Good and Varco, 1958). Unfortunately, the results went the opposite way to that intended; skin homografts survived longest on those patients who did not show any evidence of delayed allergy.

Uraemia

Skin and kidney homotransplants can survive for considerable periods, up to five months, in patients suffering from nephritis in the terminal stages (Dammin, Couch and Murray, 1957). Chemically, it has been demonstrated that urea can prevent the union of antigen and antibody *in vitro* (Nisonoff and Pressman, 1959).

Agammaglobulinaemia

One author considers that the defect in this disease lies in the inability of these patients to make *gamma*-globulin and hence being unable to make antibody, rather than the other way round (Oakley, 1959). Since these patients are unable to form antibodies to ordinary bacterial antigens, it was a logical step to investigate their reaction to skin homografts. In one case so far described, a skin homograft has survived for one year. Other prolonged survivals have been reported (Good

considerable mortality. Very soon, however, an answer to this problem was found when it was demonstrated that rats were still immunologically immature for a few days after birth (Woodruff and Simpson, 1955). Chickens also are conveniently immature for a few days after birth—usually up to about seven days (Cannon and Longmire, 1952).

Actively acquired tolerance is individually specific as indeed is transplantation immunity. The tolerance, so acquired, can be broken down by implanting into such an animal the lymph nodes removed from a sensitized animal of the same species (Medawar, 1958a). Actively acquired tolerance involves a central failure of the mechanism of immunologic response. At present, there are no visible means of exploiting this method of inducing tolerance clinically. On the one hand, the dangers of injecting the human foetus with antigenic material must make us pause; on the other hand, to challenge with an antigen immediately after birth is probably too late. Furthermore, cells of the lymphoid series must in no circumstances be used for the induction of human tolerance because of the very real danger of inducing runt or secondary disease (compare bone marrow transplantation). Search must be, and indeed is, proceeding along the lines of obtaining a cellular fraction, ribonucleic acid for example, which is capable of inducing tolerance without doing any damage to the host—otherwise there can be no future to this method (Ashley and his colleagues, 1959). Exsanguino-transfusion in the early post-natal life of dogs has been shown to be an effective method for inducing tolerance to skin homograft at a later date; the graft coming from the donor of the blood (Puza and Gombos, 1958). By this method skin grafts can survive for a period of 90 days. It is important to carry out the exsanguino-transfusion not later than the third post-natal day because skin grafts are rejected if this procedure is delayed till the seventh day. Unpublished work by the author does not confirm the results of Puza and Gombos (1958).

Splenectomy

In certain strains of mice prolonged survival of skin homografts has been reported (Werder and Hardin, 1954). No effect on homograft rejection can be detected by removing the spleen in other species. This method, then, is of no value to the clinician.

***Alpha*-globulin administration**

Prolonged survival has been induced in rats by injecting serum fractions containing *alpha*-globulins (Kamrin, 1959).

Pyridoxine deficiency

It has been demonstrated that pyridoxine deficiency can reduce serum antibody levels (Stoerk and Eisen, 1946). By creating such a vitamin deficiency in rats a prolongation of survival of skin homografts has been reported (Fisher and his colleagues, 1958). This method also suggests that homograft rejection involves an antibody response by the host, but the fact that rejection ultimately developed in spite of the lack of antibodies introduces an element of doubt about the method of rejection of homografts. This matter will be elaborated in the section dealing with kidney homotransplants (*see* page 238).

is now thought to be less specific than classical opinions allow. Indeed, the new theory of clonal selection precludes antigen from impressing its specificity on the antibody-producing cell, that is, it does not control the specificity of the antibodies. The antibody-producing cell is now widely believed to be the immature plasma cell (Nossal, 1959). The clonal selection theory claims that "the capacity to produce a given antibody is a genetically determined quality of certain clones of mesenchymal cells, the function of the antigen being to stimulate cells of these clones to proliferation and antibody formation" (Burnet, 1959). Specificity of antibody is a term which is losing its previous aesthetic attraction. One author recently pointed out that ". . . one has a tendency to forget that antibodies produced at different times of immunization differ in avidity and in flocculating power and even in their electrophoretic distribution. It is by no means impossible that tissues stimulated with antigens synthesize a great variety of *gamma*-globulins whose goodness of fit with the antigens varies enormously; those that fit well are called avid antibodies; those that fit poorly are stigmatized as non-avid, and those that do not fit at all are rejected and called *gamma*-globulin" (Oakley, 1959). This would explain why those circulating antibodies which can be demonstrated in some so-called auto-immune diseases appear not to be related to the disease at all—being merely non-specific antibodies (Anderson, Goudie and Gray, 1959). It is possible, therefore, that if circulating antibodies are demonstrated in the future in an animal carrying a skin homograft, for example, such antibodies may bear no relation to graft rejection.

The most striking difference between auto-immune disease and homograft rejection is time (Broberger and Perlmann, 1959; Thal, Murray and Egne, 1959). Diseases such as Hashimoto's disease can continue for years. Homograft rejection is over in a comparatively short space of time. Furthermore, homografts usually *undergo a process of liquefaction. Skin homografts are often seen to melt away.* Kidney homotransplants are reduced to sacs containing pus. Fragments of tissue like thyroid or adrenal are absorbed and leave no trace. Tissues involved in so-called auto-immune disease survive often repeated acute episodes and can present, in some areas of the organ, remarkably normal tissue easily recognizable as the original. This is never the case in organ homograft rejection. It may be wise not to push the kinship between so-called auto-immune disease and homograft rejection too far. There are some interesting features common to both disease systems but there are also many that do not fit.

The starting point of auto-immune disease can presumably vary considerably. The auto-antibodies associated with the haemolytic anaemias can develop after various fevers. It is often held that Hashimoto's disease results from the chronic leak of thyroglobulin which is normally cell-locked and has no access to the blood stream; in this respect it is similar to the lens of the eye. Since thyroglobulin is a protein which has not checked-in, so to speak, at the reticulo-endothelial reception depots during foetal life, it can be regarded as being virtually foreign protein. Once such a protein enters the blood stream and arrives at the reticulo-endothelial reception areas it is recognized as "not-self" and is reacted against. Antibodies to human thyroglobulin can be demonstrated but, unfortunately, do not seem to have any connexion with the disease process. What this concept

and Varco, 1955; Good and his colleagues, 1957). This condition is not due to a failure of general protein metabolism (Good and his colleagues, 1957). There are virtually no plasma cells in these patients and considering the vast accumulated evidence in favour of the antibody-producing activities of this cell, it indicates that homograft rejection is the result of an antigen-antibody reaction, and in those instances where no antibodies are produced homografts may survive indefinitely. However, the problem is not so easily resolved as that, as we will see later.

Unfortunately, the information gained from these clinical considerations cannot be exploited at the moment.

FOETAL GRAFTS

From time to time hope arises for the success of foetal grafts. Theoretically, it is hoped that foetal tissue will not evoke an antibody response and hence will not be rejected by the host. Foetal grafts of parathyroid tissue are claimed to have been successful in treating human hypoparathyroidism (Jordan, Foster and Curd, 1958). It is difficult to assess this kind of experiment because histological proof of survival has not been given; the experiment should be done in animals and proof of survival furnished. Foetal skin has not survived when homografted to an adult (Baxter and Goldstein, 1958). Foetal bone marrow, on the other hand, seems to be successful and can, to some extent, prevent the appearance of secondary disease (Barnes, Ilbery and Loutit, 1958) (*see* section on marrow grafts, page 243). Therefore, it would be wrong to rule out as useless all foetal grafts without fair trial but it should be realized at the beginning that success will be limited.

AUTO-IMMUNE DISEASE

Under normal circumstances an organism does not react against its own protein. Auto-immune disease (Kaplan and Smithers, 1959), it is thought, results when native protein in some way becomes transformed into foreign material and the organism reacts against it because it is foreign (Brent and Medawar, 1958; Burnet, 1959). The result of the interaction between antigen and antibody, it is thought, is manifested in the histological disruption of the organ or tissue concerned. The demonstration of circulating antibodies in such conditions as Hashimoto's disease, for example, appeared to prove the argument. However, some transplantation experts were sceptical because of past difficulty in demonstrating antibodies to anti-tissue antigens. Very soon it became clear that there was no correlation between the clinical state and the titre of circulating antibodies. Passive transfer of circulating antibodies, such an abysmal failure in most transplantation studies, failed to augment the experimental disease process. It is now considered that the circulating antibodies are merely by-products of the disease and not in themselves responsible for it. In transplantation studies, also, antibodies can, on certain limited occasions and in a limited number of laboratory animals, be demonstrated, but they appear not to be responsible for homograft rejection.

The significance of circulating antibody in general is changing; a recent review is most revealing about our present complete ignorance (Oakley, 1959). It should be realized that the recognition of foreign material by an organism involves a process which is not well understood. The role of the antigen in evoking antibody

homograft in its terminal phase. By observing skin grafts through a stereoscopic dissecting microscope, it can be seen that before the disintegration occurs the blood vessels to the graft become disrupted; the circulation becomes stagnant and thrombosis occurs (*compare with* kidney homotransplants, page 238). Disintegration of the homograft tends to occur about 24 hours after this vascular accident (Egdahl, Good and Varco, 1957). Some authors rely on the integrity of epithelium as an index of survival time (Billingham, Brent and Medawar, 1954). This can be quite unreliable (*compare with* homotransplanted kidneys, page 238). A more satisfactory method is that advanced by the authors who visualize proceedings through the dissecting microscope. Whether the cause of the homograft disintegration is the vascular debacle is open to doubt. Some authors consider that the epithelial destruction is well advanced within 24 hours and that the homograft rejection process has preceded it (*compare with* kidney homotransplants, page 238).

The leucocytes which are found in skin homografts vary a great deal and can include eosinophils (Roger and his colleagues, 1953), lymphocytes and plasma cells. In the past, one has considered that these cells have moved in from the host. So far as the plasma cells are concerned more critical histological work is required to establish whether they are not, in fact, arising from reticulum cells in the skin homograft itself (*compare with* kidney homotransplants, page 238). It has been shown that chicken's skin can bring about enlargement of the spleen if grafted to the chorio-allantoic membranes (Billingham and Silvers, 1959b). It is argued that this effect is brought about by an immunological reaction of the graft against antigens of the host. It is further argued that this reaction is brought about by virtue of lymphocytes in chicken skin. Since all the evidence at the moment points against lymphocytes as antibody producers one hesitates to accept this argument. It is more likely, to our way of thinking, that the reaction—if we accept this concept—is brought about by stimulated reticulum cells.

If, after an interval of time—say, seven days—a second skin homograft is applied to the same host from the same donor, a completely different history unfolds itself. Instead of becoming vascularized, it remains anaemic and lifeless, and it can be removed without any sign of bleeding from the graft bed. The graft, in fact, does not become vascularized (Egdahl, Good and Varco, 1957; Scothorne and McGregor, 1953). Again, some authors assess the survival of their second grafts by the nature of the surviving epithelium; on such a basis the survival can be extended to about six days. In fact, it is very doubtful if the second graft survives for more than 48 hours. This could be tested by transplanting the graft back at varying intervals of time to its donor site and observe whether it can establish itself again. The important point to establish here is this: is there much delay in destroying a second skin graft, because a kidney homotransplant in a sensitized animal is destroyed in a few hours. It is important to establish this point in relation to tuberculin hypersensitivity where there is a delayed reaction.

We have established, then, that a skin homograft can, in some way, sensitize an animal to a second graft from the same donor but not to that from another donor. The immunization is individual and not tissue specific. Because there is an accelerated rejection of the second skin homograft, it has been assumed that host antibodies brought about the destruction of the first. This is an assumption which

has still to demonstrate is why, after a subtotal thyroidectomy, for thyrotoxicosis, for example, when thyroglobulin must spill into the blood stream in quantity over a period of a few days, Hashimoto's disease does not invariably develop; in fact, it has never been reported in this context.

Experimentally, diseases resembling human disease syndromes can be produced by injecting extracts of tissues with a Freund adjuvant (Freund, Thompson and Lipton, 1955). How the adjuvant acts is quite unknown but without it no disease can be produced by injecting extracts of tissues. The injection of tissue extracts from an animal of another species (heterograft) can induce antibody formation. The serum withdrawn from an animal so sensitized, can now produce a specific tissue disease when injected into an animal of the first species. Thus, it is easier to produce hetero-antibodies. This is a complete mystery.

It may be that the search for auto-antibodies, *per se,* will come to nought and that sensitized cells may be demonstrated as the mediating factor in the auto-immune disease process. The role of sensitized cells in tuberculin hypersensitivity and the homograft rejection process has been discussed in the previous section.

NATURAL HISTORY OF HOMOTRANSPLANTED TISSUES

We will now pass on to consider the evidence, and a lot of it is conflicting, gained from homotransplanting different tissue systems. Since the evidence is conflicting it is perhaps too early to effect a synthesis and formulate a theory of homograft rejection which would be acceptable to all workers.

Homotransplantation of Skin

Of all the tissues in the body, skin is the one which could be used on an extensive scale in clinical practice once the rejection phenomenon was solved. Skin can be collected in limitless quantities, can be safely and easily stored at low temperatures and it can safely be removed from the cadaver. From all these points of view, skin offers greater advantages than any other tissue with perhaps the exception of bone. Yet very few plastic surgery centres have the homograft problem on their list of research activities.

Skin homografts become vascularized in much the same way as do autografts; this is usually effected by the fourth or fifth day. Because of this convenient behaviour, homografts of skin can be used as temporary dressings in severe burn injuries. However, in actual practice, such wounds are contaminated and are unsafe beds for skin grafts, therefore skin homografts are not universally popular or widely used. This is a pity because a reasonable practice of skin homografting would provide exact quantitative data about survival in man. After a period, however, depending on the individual degree of incompatibility, a homograft can resemble closely an autograft or begin to show signs of distress (acute inflammation), become turgidly swollen and disintegrate. But even the homograft which looks as if it will settle down for ever will, at some time or other in the next few days, suddenly break down, liquefy and slough off.

Once a homograft has liquefied, its histology is lost. For histological appearances one must rely on biopsies removed just before total disintegration occurs. A cellular infiltration of varying degree in the dermis is characteristic of the

later. For this reason, cadaver kidneys are not really suitable for human therapeutic purposes of an urgent nature.

(5) The remarkably prolonged survival of homotransplanted kidneys, even in genetically different individuals, following sublethal total body irradiation of the human host (Hamburger and his colleagues, 1959). Sublethal total body irradiation in the dog was not successful in prolonging survival (Dempster 1953a).

Kidney autotransplantation

Unless there be some technical reason, an autotransplanted kidney will survive indefinitely but the quality of its function will depend on the site in the body to which it is transferred.

In the larger laboratory animals, such as the dog, it is often convenient to transplant a kidney to a site which one would not consider in man. A bizarre but convenient site is the neck where the renal vessels are anastomosed to the carotido-jugular circulation and the ureter is brought out on to the skin as a ureterostomy. This site is convenient because it offers many experimental advantages. These are: the kidney can be kept under constant and direct observation, one can note readily when it ceases to function, one can remove biopsies and perform arteriograms—all with little disturbance to the animal. There is, however, a grave disadvantage *to the use of the neck as a site for the transplanted kidney. Such a "neck" kidney* is unable to concentrate urine but, in spite of this defect, a "neck" kidney can maintain life on its own very adequately (Dempster, 1950; Dempster and Joekes, 1953). It can handle sodium and potassium normally but the excretion of urea is poor. The "neck" kidney is in a constant state of polyuria (Dempster and Joekes, 1955). It is not easy to find an explanation for this functional abnormality, but the most reasonable appears to be the hydronephrosis which invariably develops to some extent in "neck" kidneys.

The functional capacity of kidneys autotransplanted to the pelvis

For the first three weeks post-operatively, a kidney autotransplanted to the pelvis using the iliac vessels for anastomosis and anastomosing the ureter to the bladder, like the "neck" kidney, is unable to concentrate urine. The cause of this immediate post-operative hyposthenuria is still obscure; there are no histological changes to account for it. After the third week, a "pelvic" kidney is able to concentrate urine normally. *The fact that a "pelvic" kidney is unable to concentrate* urine normally immediately after operation means that any definitive assessment of its function cannot be made until signs of recovery are clearly evident. Since a kidney autotransplanted to the pelvic region can recover and function normally it becomes a valid preparation for the study of the truly denervated kidney (Dempster, Joekes and Oeconomos, 1955; Dempster, Eggleton and Schuster, 1956). The fact that a "pelvic" kidney could recover normal function within a month was later confirmed by other workers (Bricker and his colleagues, 1956, 1958; Murray and his colleagues, 1956). Virtually the same operation is applicable to man and the results are satisfactory and comparable to those obtaining in the dog.

The anuric kidney

Before passing on to consider homotransplanted kidneys, it is important to be

is hard to justify when confronted with the histological appearances of kidney homotransplants in non-sensitized animals. It should be recalled here that we are still ignorant of the way in which a host rejects a homograft; we are ignorant of how the graft reacts in an immunological way to its new environment, and we do not know what happens between the time of rejection of the first homograft and the application of the second.

Transplantation of Kidney

One can rejoice in the fact that kidneys exchanged between human identical twins have been effected with success in a few cases (Murray, Merrill and Harrison, 1958). This is the culmination of many years work on the genetical laws of tissue transplantation. One can enthusiastically salute the surgeons who successfully performed the operations and also the healthy twins who submitted themselves to the operations. There is, however, one unfortunate drawback to work of this nature. It has been found that the healthy transplanted kidney can quickly succumb to the very nephritic process which destroyed the kidneys of the ill twin in the first place. This is a very bitter pill to swallow indeed. It has its interesting side, of course. There is also a report that a kidney from a genetically unrelated individual can become involved in a nephritic process if transplanted to a nephritic person (Hume, Merrill and Miller, 1955). The exact histological details of both these reports have not yet been published. If substantiated, they suggest very strongly that human nephritis is produced by some circulating factor which is tissue specific and not individual specific—as in transplantation immunity. It has been reported that by giving sublethal doses of x-irradiation the nephritic process can be so damped down as to allow normal survival of a transplanted kidney. If this can be substantiated, it would indicate that nephritis itself should be treated by x-irradiation since some unknown humoral factors are presumably destroyed by this agent.

It is now proposed to review briefly our knowledge about the behaviour of the autotransplanted kidney so that we can the more adequately control the results with homotransplanted kidneys. Obviously, this sort of work can only be adequately done in the larger laboratory animals. Indeed, little more has emerged from the work on human beings than was already well established in laboratory animals. The interesting and new features which have emerged from human studies are as follows.

(1) The prolonged survivals in recipients suffering from chronic nephritis (Hume, Merrill and Miller, 1955).

(2) The remarkable survival of kidneys exchanged between non-identical twins together with the fact that in one case a skin graft was rejected before the kidney transplant; both tissues had come from the same non-identical brother twin (Hamburger and his colleagues, 1959; Murray, Merrill and Harrison, 1960).

(3) The reported claim that nephritis can develop in a transplanted kidney indicating that tissue specific agencies are responsible for the onset of nephritis in man (Hume, Merrill and Miller, 1959).

(4) The remarkable behaviour of a homotransplanted kidney removed from a cadaver (Hume, Merrill and Miller, 1955). Such a kidney seldom secretes immediately after establishing the new circulation but may become established some days

what the cause of arrest of function is. It is all very well to invoke an immunological cause but it is not easy to support this concept with facts. This being the situation, it is necessary to state facts about the evolution of histological changes in homotransplanted kidneys before one makes assessment of the problem at all.

The evolution of histological changes in homotransplanted kidneys

Homotransplanted kidneys which are removed on the third and fourth day after operation, while still secreting, show remarkably little histological alteration (Dempster, 1955b). There is some separation of the tubules due to oedema and this is consistent with the finding that these kidneys begin to swell in the first 72 hours. With adequate pyronine stains one can discern curious star-shaped cells in the interstitium of these kidneys and, in some cases, one can distinguish cells resembling the transitional cells of Fagraeus (Darmady, Dempster and Stannock, 1955; Dempster, 1953a; Hume and Egdahl, 1955; Humphries, 1956; Simonsen and his colleagues, 1953).

To obtain good histological material from homotransplanted kidneys which have suddenly become anuric, one must remove them as soon as possible after the onset of anuria. It is essential to remove the homotransplanted kidneys early because quite quickly a process of liquefaction ensues which can render any histological interpretation valueless after 36 hours or so. Depending on the interval between the onset of anuria and the removal of homotransplanted kidneys there are three main histological stages.

(1) Little tubular damage can be discerned in homotransplanted kidneys which have been removed within six hours of the onset of anuria. A nephron dissection of the tubules reveals an area of atrophy and collapse in the neck of the tubule (Darmady, Dempster and Stannock, 1955). On careful histological investigation one can demonstrate such lesions but they are not easily seen unless consciously looked for. The area of the tubule affected is collapsed and the epithelium is translucent. The remainder of the tubule appears essentially normal. In the interstitium, however, there is marked oedema and a massive infiltration of pyronine o-staining cells. These cells are, in the main, immature plasma cells (Fagraeus, 1948). These cells have evolved from the reticulum cells of the homotransplanted kidneys themselves. A clear demonstration of the evolution of these cells has been made (Darmady, Dempster and Stannock, 1955).

(2) If a homotransplanted kidney is not removed until 24 hours after the onset of anuria, the histological appearance is that of commencing disintegration. Many tubules are necrotic and some areas have disappeared. The cellular infiltration has changed from a purely pyronine-staining cell to a collection of polymorphs and macrophages. The glomeruli remain remarkably normal (Dempster, 1957).

(3) If 48 hours pass before the anuric homotransplanted kidney is removed, the histological picture is that of very advanced disintegration. The parenchyma has largely melted away in a mass of polymorphs and macrophages.

This rather artificial staging of the histological process can only be adequately worked out in dogs. It is of some practical importance to be aware of this evolution of events in trying to assess the cause of anuria (Dempster, 1957). If one were ignorant of the histological situation described in the first stage, one would be

aware of certain technical problems which can confuse experimental work. From time to time in both autotransplanted and homotransplanted kidneys, an immediate post-operative anuria ensues (Dempster, 1954a). This phenomenon has been referred to as the anuric kidney. It is most important to be aware of this technical complication and to be *au fait* with the histological appearances of such kidneys, because immunological considerations are not involved. In dogs, the complication is irreversible and it is rare to be able to retain such a kidney *in situ* beyond the fourth post-operative day, because by that time the kidney is swollen and its odour is extremely offensive. In man, presumably because of better control of infection, anuric kidneys can survive without infection for some weeks and they may start to function at a later date. Some authors (Egdahl and Hume, 1956) discounted the importance of this complication but it should be kept in mind lest it complicate any immunological considerations. When cadaveric human kidneys are used they are invariably anuric after the operation. Other workers have attempted to modify the natural history of kidney homotransplants by inducing impairment of renal function prior to the transfer (Lang, Murray and Miller, 1956). This attempt was not successful.

Homotransplanted kidneys

The natural history of homotransplanted kidneys in dogs follows a fairly well-defined course. It starts to secrete within a few minutes of establishing its new circulation. It then rapidly enlarges to twice or three times its previous weight within 72 hours (Dempster, 1955b). An autotransplant will enlarge to a considerably smaller extent in the same time and the enlargement in this case is probably due to the cutting of lymphatic trunks and the general trauma of mobilization. The increase in weight which develops in the course of time is due to hypertrophy. Such a kidney can reduce post-nephrectomy hypertension (Muirhead and his colleagues, 1956). One day, after a period of quite adequate function, a homotransplanted kidney suddenly ceases function (Dempster, 1953a, 1955b; Hume and Egdahl, 1955; Humphries, 1956). The period of survival of a large series of homotransplanted kidneys is variable but it is usually within three weeks. In this respect, the life history resembles very closely that of a normal human homotransplanted kidney (Michon and his colleagues, 1953). However, when a human host is a chronic nephritic, the period of survival may extend to months (Owen, 1945; Hume, Merrill and Miller, 1955). Another feature common to normal dogs and human beings is the dramatic suddenness of the onset of anuria. An arteriogram taken soon after the onset of anuria in dog homotransplanted kidney reveals an intense and widespread vascular spasm within the kidney (Dempster, 1955b). At about the time of the onset of the anuria, the host shows signs of toxicity; this has been referred to as the toxic syndrome and is usually a reliable clinical guide to the onset of anuria.

The functional arrest of homotransplanted kidneys

It is not possible to assess accurately the cause of arrest of function of homotransplanted kidneys without detailed knowledge of the evolution of the histological features. Because of the rather superficial data which we have at our disposal at the moment, it is not yet possible to state, with any degree of confidence,

to be gross enough to bring about complete anuria in so dramatic a manner and, yet, we know that in the kidney rendered anuric by sulphanilamides there is often remarkably little to see histologically. Therefore, it could be argued that a homotransplanted kidney might be rendered anuric by quite a mild antibody reaction from a host. It is a mild reaction so far as cell damage is concerned. Some workers have shown that there is no increased histamine content in transplanted kidneys (Nathan and Miller, 1958). One has to consider, however, whether the normally large content of histaminase in the kidney prevents any tissue manifestation of any small increase of histamine. There is little more oedema on the day that a homotransplanted kidney ceases to function than on the third post-operative day. The cause of this early oedema has not yet been determined but it seems that it is an early reaction on the part of a homotransplanted kidney to some cytotoxin of host origin. It must be admitted that clinical glomerulo-nephritis bears no histological relationship to a rejected kidney homotransplant.

One could argue, also, that since hetero-antigens and hetero-antibodies are used in experimental nephritis, and hetero-antigens, in the form of bacteria, may be involved in the clinical forms of glomerulo-nephritis, that our preceding criteria are not valid for homo-antigen-antibody reactions. However, one can produce unequivocal evidence that when an antigen-antibody reaction does occur in a homotransplanted kidney, the nature of the tissue damage and the site of reaction correspond to the criteria derived from clinical and experimental data. One can produce this evidence as follows: after a homotransplanted kidney has ceased to function it is removed from its host. After an interval of about seven days, the second kidney from the same donor is transplanted to the same host as received the first kidney. Within a few hours of effecting this transfer, the second kidney ceases to function and the histological features are those of a severe acute antigen-antibody reaction (Dempster, 1953a). There is no doubt that in this second experiment the host has produced antibodies of great avidity.

Some circumstantial evidence indicates that perhaps host antibodies may not be involved against first homotransplanted kidneys.

(1) Histological evidence of renal antigen-antibody reactions in first kidneys is not detectable or obvious (Dempster, 1953a). No trace of antibody has been detected by the Coons technique (Fisher and Fisher, 1959).

(2) Total-body irradiation of a host in no way modifies the natural history of a kidney homotransplant (Dempster, 1953a). Properdin administration has no effect either (Hubay and Persky, 1957).

(3) A kidney which after four (Simonsen and his colleagues, 1953) or two (Dempster, 1955b) days in a foreign host is transferred back to the original owner will continue to secrete for several days and then quite suddenly will cease functioning. The histological features of this homo-autotransplanted kidney resemble in every way those of the homotransplanted kidney. Host antibodies cannot be claimed to have caused the arrest of function in this case. The natural history suggests, however, that after about 48 hours in a foreign host a homotransplanted kidney is in some way stimulated to pass through a course of cellular change over which it has no control, even when it is removed from a foreign environment (Dempster, 1955b).

inclined to assume that infection brought about the arrest of function. Indeed, this explanation held the field for many years. But it is the histological picture in stage 1 which must be given the main emphasis in assessing the cause of anuria.

An assessment of the cause of arrest of function

(1) *Increased interstitial pressure caused by oedema* is not likely to prove important since the tubules show no signs of collapse.

(2) *Hydronephrosis* is unlikely to be a cause of functional arrest since it occurs in autotransplanted kidneys.

(3) *The lesion localized to the region of the tubule neck* is unlikely to be the cause since this can be abolished by cortisone administered throughout the course of the homotransplanted kidney's survival.

(4) *The immature plasma cell infiltration* is not likely to be the cause of anuria since one can abolish the infiltration, by x-irradiation (Dempster, 1953a), and cortisone (Dempster, 1953c), without prolonging the survival time of homotranspanted kidneys.

(5) *Vascular spasm* is very marked in a homotransplanted kidney which has just entered the anuric phase (Dempster, 1955b). Cortisone can, to some extent, reduce the vascular spasm but without prolonging survival (Dempster, 1953c). Vascular spasm is, however, closely associated with whatever other event takes place in the phase preceding the onset of anuria.

(6) *Host antibodies:* it is widely accepted today that the cause of homotissue disintegration is the development, in a host, of an actively acquired immunity. There is a fair amount of evidence to support this view, but so far as homotransplanted kidneys are concerned evidence is meagre unless one makes considerable assumptions and inferences. It will be important, therefore, to consider what the available information is concerning antigen-antibody reactions in kidneys.

Renal antigen-antibody reactions

For a long time it has been considered, from indirect evidence, that antigen-antibody reactions are concerned in such diseases as glomerulo-nephritis and periarteritis nodosa. The nature of these reactions was obscure. Some authors have demonstrated that *gamma*-globulins actually are present in the glomerular lesions in glomerulo-nephritis and in the medial coat in periarteritis nodosa (Mellors and Ortega, 1956). It is generally agreed that a mild reaction produces endothelial proliferation of the glomerular tuft and that a severe reaction produces wholesale tissue damage in the course of which the glomerular tufts become disrupted allowing protein to leak into the lumen of the tubule. A range of intermediate reactions can be described. Other than these two main groups of lesions—glomerular and fibrinoid deposits in the medial coat of arteries—there are no other known types of lesions associated with renal antigen-antibody reactions.

The kidney is well known for its ability to react to a variety of toxins in remarkably similar manner. However, no histological sign of an antigen-antibody reaction can be found in anuric homotransplanted kidneys. Most workers agree that the tufts are remarkably normal and most agree that there is no fibrinoid change in the medial coat of the renal vessels. The histological changes in stage 1 appear not

fit into a common pattern in their behaviour towards their hosts. This in many ways complicates the whole problem.

The possible use of organ homotransplants in the forseeable future forces one to consider ways and means of preserving organs for future use. The two main techniques which will occupy interest in the future will be hypothermia and pump perfusion. An attempt (Couch, Cassie and Murray, 1958) at the latter has recently been reported but there are obviously many more problems to solve before such perfusion systems can be of any practical use.

Total-body irradiation and kidney transplantation

Total-body irradiation of a host dog was found by one worker to have no effect on the natural history of a homotransplanted kidney (Dempster, 1953a). A lethal dose of irradiation can now be given and followed up by the infusion of bone marrow cells (Congdon, Uphoff and Lorenz, 1952). These cells repopulate the animal and prevent radiation death. One group of workers has now gone one stage further. They have transplanted a kidney from the same animal which donated the bone marrow cells. This kidney survived normally for 49 days before the animal died of an intercurrent infection (Mannick and his colleagues, 1959). There was no indication of a plasma-cell infiltration at necropsy—a fact which led the investigators to question the renal origin of the immature plasma cells invariably seen in kidneys homotransplanted to normal hosts. Since no plasma cells were seen in this kidney, it could mean that Simonsen's concept of their origin is correct (Simonsen and his colleagues, 1953). His attitude is that the reticulum cells of a homotransplanted kidney fix host antibody and in turn produce anti-antibody. This, according to Simonsen is a response not to host antigen but to host antibody; a criticism of this concept is presented elsewhere (Dempster, 1955b). However, not enough facts are known about total-body irradiation to enable us to understand why the kidney in the above-mentioned case did not react to host antigens. Under normal circumstances kidneys can, in cases of pyelonephritis for example, produce plasma cells and so the kidney can defend itself under duress.

BONE MARROW TRANSPLANTATION

The consequences of total-body irradiation are now well established (Barnes and Loutit, 1959; Congdon, Uphoff and Lorenz, 1952; Ferrebee and his colleagues, 1958). Within a short interval of time there is an impaired cell division manifested first in those tissues where cells normally are undergoing rapid division. Extremely high doses of total-body irradiation lead to acute cell death and injury of all tissues in the body. Irradiation in the range 300–700 roentgen leads to bone marrow failure, loss of platelets and circulating blood cells, bleeding and infection, loss of the lymphoid tissues, diarrhoea and overwhelming infections.

This type of irradiation death can be prevented by infusing viable bone marrow cells into irradiated animals; such animals are termed chimaeras (Congdon, Uphoff and Lorenz, 1952; Makinodan, 1957). Techniques for collecting and storing bone marrow are now well established (Ferrebee and his colleagues, 1959). If the irradiation has not been completely effective in destroying the lymphoid cells of the animal, regeneration of these cells occurs which will destroy the remaining grafted bone marrow cells. A recent report, involving accidental irradiation of

(4) It has been shown that if a second kidney is transplanted to an animal on the very day that a first kidney is rejected, the second kidney will continue to function for several days (Gordon and Richards, 1957). If the first kidney succumbed to host antibody one would expect the second kidney to succumb quickly to this same factor. The author's unpublished results would only partly confirm the reported results of this type of experiment. Skin homografts do not appear to behave in the above manner (Lehrfeld, Taylor and Converse, 1954).

(5) One does not know for certain what the antigen of a homotransplanted kidney is nor how it escapes from a homotransplanted kidney in a host (Goodman, Greanspon and Krakower, 1955; Hill and Cruickshank, 1953). One might assume that the elimination of antigen via the renal vein is a continuous process. If this be true there is evidence to show that antibody production in an animal is embarrassed so long as antigen remains in the blood stream. Some work indicates that the elimination of antigen from the blood stream precedes the appearance of antibody (Talmadge and his colleagues, 1951). This *might indicate that so long as a homotransplanted kidney is part of the vascular system of a host, antibody production by that host may be embarrassed.*

(6) No significant decline in the level of complement has been detected after the rejection of a canine kidney homotransplant (Favour and his colleagues, 1953).

(7) Kidney homotransplants may not be subjected to the same laws as other tissues. There are reports of human cases (Kuss and his colleagues, 1960) in whom skin homografts have been rejected while a kidney homotransplant from the same donor has continued to survive.

Since there is no histological evidence of an antigen-antibody reaction in first homotransplanted kidneys but there is histological evidence of an acute severe reaction in second homotransplanted kidneys, one is entitled to ask whether the host is alone responsible for the disintegration of first kidneys. It is possible to argue that a homotransplanted kidney, in attempting to defend itself against host antigen, brings about its own destruction (Dempster, 1955b). At the same time host antibodies are in production, but only after the removal of the first kidney is a host in a position to produce antibodies of great avidity which are immediately deployed against a second challenge of tissue from the same donor. The autodestruction suggested above may be brought about by a sudden biochemical lesion because there is little sign of tubular damage prior to the onset of anuria, that is, there is no glycosuria, no increased amino-aciduria and no increased proteinuria.

Until recently the theory of actively acquired immunity attempted to explain the whole process of homograft disintegration in terms of a host reaction. Histological evidence in first homotransplanted kidneys suggests that the kidney itself might be producing antibodies against the host by virtue of the immature plasma cells evolving in vast numbers in the interstitium of the kidney (Dempster, 1953a, 1955b). It has not yet been proved that antibodies are actually produced. Some workers claim that the red cells of animals receiving homotransplanted kidneys become Coombs positive (Muirhead and Groves, 1955). If this claim can be confirmed, it would suggest antibody formation on the part of homotransplanted kidneys. The ability of a graft to react against its host has been proved for systems involving bone marrow homografts. In time, it may be proved that all homografts

tolerant to the host tissues (Barnes, Ilbery and Loutit, 1958). However, even animals injected with foetal cells at some time or other may enter the phase of secondary disease. In such cases, foetal marrow merely delays the fatal issue. The decline in the number of cells populating the lymph nodes, spleen and bone marrow is associated with wasting due probably to malabsorption and ill-health on the part of the animal. Diarrhoea, bleeding due to lysis of red cells and infection due to loss of some defence mechanisms in the homografted marrow lead at some time or other to death of the animal; the loss of the defence mechanisms is not seen in isografts of marrow so that this implies that the graft, *per se*, is not deficient in such defence mechanisms. A similar type of disease is well-known in pigs and cattle and this is called runt disease. Animals rendered tolerant by intrafoetal injections of tissue, when mature, also show signs of this disease (Billingham, Brent and Medawar, 1953; Brent and Medawar, 1958). In all these diseases—runt, secondary, homologous or F_1 hybrid disease (Grabar and his colleagues, 1958)—there is a common factor, and that is the presentation of foreign cells into an immunologically inactive or paralysed animal.

The decline in the cells populating the lymphoid tissue leads to necrosis, fibrin deposits and fibrous tissue. Finally, the nodes are enlarged but contain only fibrin, necrotic cells and fibrous tissue. The dead cells are those derived from the graft marrow. In addition, there are areas of necrosis in the bowel and in the liver and here the cells are host cells. Elsewhere, infection has so complicated the picture that it is difficult to be sure what the underlying process has been. The cause of death is probably infection brought on by the disintegration of the lymphoid areas.

Secondary disease

Secondary disease has been considered to result from a reaction of the grafted cells against the host antigens (Feldman and Yaffe, 1958; Gordon and Richards, 1957; Hamburger and his colleagues, 1959; Uphoff and Law, 1958; Werder and Hardin, 1954). It is very doubtful if these authors have, in fact, demonstrated that a graft-against-host reaction exists. All that has been shown is that lymphoid cells injected into an immunologically inactive or paralysed animal can be lethal. If at any time one can show that cell extracts can produce secondary disease, the concept of a graft-against-host reaction, in this context, must be withdrawn.

The demonstration, by some authors, of rat *gamma*-globulin in mouse serum is interesting; its significance remains to be determined but there is no evidence that this *gamma*-globulin causes the mouse any distress (Grabar and his colleagues, 1958). So far as homografts of bone marrow are concerned, there is no evidence that they cause the host any harm. The decline in health occurs when the lymphoid cells are destroyed and not because the grafted cells destroy host cells. It has been considered that the concentration of host antigen becomes so overwhelming that the grafted cells die as a direct result of trying to deal with the situation (Grabar and his colleagues, 1958). However, before accepting this interpretation one should inquire if at any time in the natural history of the grafted cells there have been any histological signs in the graft cells comparable to those well-known to occur in animals subjected to hyperimmunization. One would require evidence of massive immature plasma-cell concentrations in the bone

several men, indicates that this sort of outcome was responsible for their restoration to health (Mathé and his colleagues, 1959). It is possible, therefore, that bone marrow injections may be indicated in the future as a life-saving measure to tide a patient over until his own lymphoid tissues resume their activity. If, however, the dose of irradiation is effective in destroying the lymphoid tissue of an animal, bone marrow cells infused into such an animal will settle in the depleted marrow and lymphoid tissue areas, will multiply and finally colonize these areas and will provide the white cells circulating in the blood stream, Female marrow is usually injected into male recipients. This makes it easier to detect foreign cells since the female chromatin marker in the polymorphonuclear leucocytes is very obvious. It has been suggested that it is easier to trace the female marker in the polymorphonuclear leucocytes if a smear from the haematocrit buffy coat is used (Porter, 1957).

Complete protection can be effected if the marrow is donated from an individual of the same genetic pattern (Barnes, Ilbery and Loutit, 1958). If the marrow is donated from a genetically unrelated individual, only a temporary reprieve may be effected. Such an animal may suffer one of several fates: it may die at a later stage from several disorders collectively known as secondary disease, it may become a red or white cell chimaera, or it may survive normally for a considerable period.

Lethal doses of total-body irradiation followed by successful replacement of bone marrow cells is a relatively easy procedure in rodents. In larger animals, such as dog and man, many factors interfere with a smooth post-irradiation course. By far the most important of these is infection. In addition, the reticulo-endothelial system of the dog appears to be rather insensitive to the effects of irradiation (Ferrebee and his colleagues, 1959). Infection occurs sooner or later in most species so far studied and is probably responsible for the diarrhoea reported by some workers. Infection can occur in spite of an adequate leucocytosis, and is the factor thought to be responsible usually for the deaths of animals suffering from secondary disease. To what extent death is due to an inadequate lymphoid system has yet to be determined. We will now discuss the effects on the lymphoid system in an animal which has received total-body irradiation and has been successfully infused with bone marrow cells.

The lymphoid system in an irradiated and marrow-infused animal

The natural history of the lymphoid system of an irradiated animal is as follows: death of the lymphoid cell occurs at varying intervals so that by the time the bone marrow cells are infused the lymphoid depots are virtually depleted. The injected marrow cells settle in various sites of the body and quickly regenerate and provide the cells of the circulating blood. The colonization of the lymphoid areas is slow and is seldom complete, that is, although the lymph nodes, spleen, and so forth, are repopulated there is still room for the normal complement of cells; the pulp centres do not regenerate (Congdon, Uphoff and Lorenz, 1952). In the first phase of regeneration in the lymph nodes one can demonstrate cells of the Fagraeus cycle, lymphocytes, macrophages and the usual cells in the peripheral blood. According to the maturity of the injected bone marrow cells so they gradually decline. Foetal bone marrow cells endure longer than adult cells because it is thought that by the time they have become mature they have been rendered

Having defined what was originally meant by a graft-against-host reaction let us now examine the claim that secondary disease is due to the reaction of a bone marrow graft against a host. From all the histological evidence it would appear that grafted bone marrow cells die in the lymphoid areas although the bone marrow cells and circulating white cells appear to be still present in reasonably normal numbers and indeed, a leucocytosis can occur; this indicates that the marrow cells are still active. What is the reason for the death of the colonizing cells in the lymph nodes and spleen? It is widely held that this is a graft-against-host reaction. But if it were a graft-against-host reaction one would expect signs of hyperimmunization in these areas. This does not occur and the evidence points to some cytotoxic element in the host bringing about death of *grafted cells* in lymphoid areas. Death of the animal may be due to lack of lymphoid tissue, because the marrow cells are still intact. It is possible, therefore, for an immunological cripple to reject a homograft settled in its lymphoid areas but apparently *not in its marrow*. This might indicate that all homografts in normal animals are rejected by a similar process which does not involve host antibodies but other undefined host cytotoxins. It would be easier to explain the rejection of a homotransplanted kidney on such a basis.

Immunological reasons aside, it is quite possible that there are several factors contributing to secondary disease in radiation chimaeras—late radiation damage and an impaired anti-bacterial defence system.

Although there seems little hope of applying x-irradiation and bone marrow grafts to clinical purposes, this is a valuable approach to homograft problems. It is possible that part removal of a person's own bone marrow followed by x-irradiation and return of the marrow may be of value in treating certain types of cancer.

Transplantation of Endocrine Tissue and Halsted's Law

A great deal of confusion has developed since Halsted concluded, following some experiments on dogs, that parathyroid tissue implanted in excess of what is urgently required by the organism does not live, and that a deficiency greater than half must be created before auto-implanted parathyroid survives (Halsted, 1909). These conclusions were not confirmed by later studies (Dempster, 1954b; Dempster and Doniach, 1954; Shambaugh, 1936). Numerous experiments over the years have shown that auto-implants of thyroid tissues have survived in animals not suffering from any gross thyroid deficiency. Nevertheless, the confusion remains in the minds of some individuals. The misunderstanding appears to have arisen chiefly through failure to differentiate and evaluate the various stages of survival of an implant (Dempster and Doniach, 1954). An implant, as distinct from a transplant, is a fragment of tissue transferred without a blood supply and is dependent on a future existence upon the speed of revascularization which the host can effect. The various stages of survival are as follows.

(1) The immediate death of the main mass of implants more than 300 microns in diameter and the survival of peripherally-placed cells.

(2) Proliferation of surviving cells in association with proliferation of local blood vessels (revascularization) which form a fixed pattern typical of tissue implanted.

(3) The formation of a functioning implant responsive to physiological stimuli.

marrow and other areas; some authors have reported that even the adrenal glands in normal animals can participate in producing plasma cells. There are some signs in the early stages following infusion of bone marrow, of plasma-cell concentrations in the bone marrowspaces and elsewhere but this could quite well be explained by the fact that the grafted cells were in an active stage of regeneration.

There would not appear to be any reports suggestive of a phase of hyperimmunization in the lymph nodes which one must expect if the host antigen is constantly activating the grafted cells. If this did occur one could concede that the grafted cells respond at first to host antigen (that is, a graft-against-host reaction) and later disintegrate in the face of overwhelming concentrations. However, on the present available evidence there is no data to support such a concept. On the contrary, it is exactly during the period of active regeneration of grafted cells, when one would expect their immunological vigour to be at their peak, that the animal is in a state of well-being. It is during the phase of decline of the lymphoid cells in the lymph nodes and elsewhere that emaciation, diarrhoea and infection occur. It cannot possibly be maintained that the grafted cells are reacting (that is, producing antibodies) against host antigens and so undermining the health of the host animal which is what a graft-against-host reaction would mean when, in fact, the host succumbs to its having destroyed the very cells which maintained it healthy in the first phase after irradiation. What the evidence does indicate is this: the grafted cells survive for a while and then are destroyed in the lymphoid areas.

What the cytotoxic agent is has not yet been made clear. Since we assume that the host is an immunological cripple it cannot be by viture of host antibodies. Then presumably the grafted cells die because of some cytotoxic action of host antigen. Some authors partly concede this (Barnes and Loutit, 1959; Gorer and Boyse, 1959). This is exactly the reasoning behind the present author's interpretation of the rejection process in homotransplanted kidneys and, indeed, in all homografts. Homotransplanted kidneys are not destroyed by host antibody but by host antigen which has a powerful cumulative cytotoxic activity.

To talk of a graft-against-host reaction has now become quite fashionable. In the original papers (Dempster, 1953a; Simonsen, 1953) describing a graft-against-host reaction two distinct concepts were put forward. The first (Simonsen, 1953, 1955), the more complicated and more imaginative, suggested that host antibodies develop within a few hours, pass through the well-known sites of union with antigen and fix on the reticulum cells of the transplanted kidney. These reticulum cells then evolve into immature plasma cells and in doing so produce anti-antibody. The other suggestion (Dempster, 1953a) was that host antigen, whose nature is still undetermined, evoked the plasma-cell reaction; in a subsequent article reasons for rejection of the anti-antibody concept have been given (Dempster, 1955b). But both Dempster and Simonsen have demonstrated that the homotransplanted kidney produces immature plasma cells. On this basis, and the evidence would appear to be self-explanatory to those aware of the significance of immature plasma cells, a graft-against-host reaction was formulated. This concept was an advance on the previous attitude to the problem in so far as a homograft was regarded as a passive, immunologically inactive structure awaiting inevitable death at the moment host antibodies attacked it.

Billingham, R. E., Brent, L., and Medawar, P. B. (1953). "Actively Acquired Tolerance of Foreign Cells". *Nature, Lond.*, **172**, 603.
— — — (1954). "Quantitative Studies on Tissue Transplantation Immunity". *Proc. roy. Soc., B.*, **143**, 58.
— Krohn, P. L., and Medawar, P. B. (1951). "Effect of Cortisone on Survival of Skin Homografts in Rabbits". *Brit. med. J.*, **1**, 1157.
— Lampkin, G. H., Medawar, P. B., and Williams, H. L. (1952). "Tolerance to Homografts, Twin Diagnosis, and the Freemartin Condition in Cattle". *Heredity*, **6**, 201.
Bollag, W. (1956). "Nachweis von individual spezifischen gervelsanti Körpern". *Experientia*, **12**, 57.
Brent, L., and Medawar, P. B. (1958). "Tolerance and Auto-immune Phenomena". In *Recent Progress in Microbiology*. p. 181. Oxford; Blackwell.
— Brown, J., and Medawar, P. B. (1958). "Skin Transplantation Immunity in Relation to Hypersensitivity". *Lancet*, **2**, 561.
Bricker, N. S., Guild, W. R., Rearden, J. B., and Nevill, J. P. (1956). "Studies on the Functional Capacity of a Denervated Homotransplanted Kidney in an Identical Twin with Parallel Observations in the Donor". *J. clin. Invest.*, **35**, 1364.
— Straffon, R. A., Mahoney, E. P., and Merrill, J. P. (1958). "The Functional Capacity of the Kidney Denervated by Autotransplantation in the Dog". *Ibid.*, **37**, 185.
Broberger, O., and Perlmann, P. (1959). "Auto-antibodies in Human Ulcerative Colitis". *J. exp. Med.*, **110**, 657.
Burnet, M. (1959). "Auto-immune Disease". *Brit. med. J.*, **2**, 645.
Calne, R. Y. (1960). "The Rejection of Renal Homografts. Inhibition in Dogs by 6-mercaptopurine". *Lancet*, **1**, 417.
Cannon, J. A., and Longmire, W. P. (1952). "Studies of Successful Skin Homografts in the Chicken: Description of a Method of Grafting and its Application as a Technic of Investigation". *Amer. J. Surg.*, **135**, 60.
Congdon, C. C., Uphoff, D., and Lorenz, E. (1952). "Modification of Acute Irradiation Injury in Mice and Guinea-pigs by Injection of Bone Marrow: a Histopathologic Study". *J. Nat. Cancer Inst.*, **13**, 73.
Couch, N. P., Cassie, G. P., and Murray, J. E. (1958). "Survival of the Excised Dog Kidney Perfused in a Pump-oxygenator System". *Surgery*, **44**, 666.
Craddock, C. G., and Lawrence, J. S. (1948). "The Effect of Roentgen Irradiation on Antibody Formation in Rabbits". *J. Immunol.*, **60**, 241.
Dammin, G. J., Couch, N. P. and Murray, J. E. (1957). "Prolonged Survival of Skin Homografts in Uraemic Patients". *Ann. N. Y. Acad. Sci.*, **64**, 967.
Darmady, E. M., Dempster, W. J., and Stannock, F. (1955). "Evolution of Interstitial and Tubular Changes in Homotransplanted Kidneys". *J. Path. Bact.*, **70**, 225.
Dempster, W. J. (1950). "Observations on the Behaviour of the Transplanted Kidney in Dogs". *Ann. R. Coll. Surg. Engl.*, **7**, 275.
— (1951). "Problems Involved in the Homotransplantation of Tissues, with Particular Reference to Skin". *Brit. med. J.*, **2**, 1041.
— (1953a). "Kidney Homotransplantation". *Brit. J. Surg.*, **40**, 447.
— (1953b). "A Toxic Syndrome Observed in Dogs with Transplanted Kidneys". *Acta med. scand.*, **144**, 360.
— (1953c). "The Effect of Cortisone on the Homotransplanted Kidney". *Arch. int. Pharmacodyn.*, **95**, 253.
— (1954a). "The Anurias Following Kidney Transplantation". *Acta med. scand.*, **147**, 91.
— (1954b). "Halsted's Law and the Regeneration of Organs". *XVth Inter. Chir. Congress.* p. 933.
— (1954c). "A Technique for the Study of the Behaviour of the Autotransplanted Kidney, Adrenal and Ovary". *J. Physiol.*, 124, 15P.
— (1955a). "The Transplanted Adrenal Gland". *Brit. J. Surg.*, **42**, 540.

Thus, a surviving thyroid implant, for example, seen in stage 3 will be very much larger and more active in a totally thyroidectomized than in a non-thyroidectomized animal, not because it is more successful but because it has responded to the physiological stimulus of thyroid deficiency. A successful implant in a euthyroid animal might even be overlooked unless stimulated to further growth by thyroidectomy.

Instead of implanting endocrine tissue one transplants a whole gland such as the adrenal or ovary, Halsted's law at once becomes quite meaningless. The key to the whole problem is blood. By transplanting an adrenal gland with its adjacent kidney, one obtains a preparation which begins to function as soon as the new blood supply is established, which survives and which can maintain life when the contralateral gland is removed at a later date. Such a transplanted organ is not required to regenerate because of prior necrosis; it is left mainly intact after transplantation—provided the renal artery branches are adequate. The ease with which rodents can revascularize implants of endocrine tissue is a blessing for the experimental biologist but sheds little light on problems in larger mammals.

CONCLUSION

The possibility of a break through on the homograft problem in the near future is hardly likely. Perhaps the most important step forward would be a synthesis of all the available and apparently contradictory data into a co-ordinated account of why tissues exchanged between individuals are rejected. It is quite possible that the problem will be solved clinically long before the mechanism of rejection is thoroughly understood. Interest in the future should concentrate on the remarkable effects of sublethal total body irradiation in prolonging the survival of kidney homotransplants in man.

REFERENCES

Amos, D. B., Gorer, P. A., Mikulska, B. M., Billingham, R. E., and Sparrow, E. M. (1954). "An Antibody Response to Skin Homografts in Mice". *Brit. J. exp. Path.*, 35, 203.

Anderson, J. R., Goudie, R. B., and Gray, K. G. (1959). "Complement-fixing Auto-antibody to Thyroglobulin in Hashimoto's Disease". *Lancet*, 1, 644.

Ashley, F. L., McNall, E. G., Garcia, E. N., Sloan, R. F., and Edwards, J. W. (1959). "Studies on Mammalian Homotransplants of Skin. iii. An Attempt to Induce Tolerance Across the Placenta in Rats with RNA and DNA". *Amer. J. Surg.*, 98, 217.

Baker, R., Gordon, R., Huffer, J., and Miller, G. H. (1952). "Experimental Renal Transplantation 1. Effect of Nitrogen Mustard, Cortisone and Splenectomy". *Arch. Surg.*, 65, 702.

Barnes, D. W. H., and Loutit, J. F. (1959). "Immunological Status and Longevity of Radiation-chimaeras". *Proc. roy. Soc.*, *B.*, 150, 131.

— Ilbery, P. L. T., and Loutit, J. E. (1958). "Avoidance of 'Secondary Disease' in Radiation Chimaeras". *Nature, Lond.*, 181, 488.

Baxter, A., and Goldstein, M. A. (1958). "Simultaneous Grafting of Skin from Identical Foetal Twins to an Adult". *Transpl. Bull.*, 5, 63.

Billingham, R. E., and Silvers, W. K. (1959a). "Inbred Animals and Tissue Transplantation Immunity". *Transpl. Bull.*, 6, 399.

— — (1959b). "Immunologic Competence of Chicken Skin". *J. Immunol.*, 82, 448.

— and Sparrow, E. M. (1955). "The Effect of Prior Intravenous Injections of Dissociated Epidermal Cells and Blood on the Survival of Skin Homografts in Rabbits". *J. Embryol. exper. Morphol.*, 3, 266.

Gengozian, N., and Makinodan, T. (1956). "Antibody Response of Lethally X-irradiated Mice Treated with Rat Bone Marrow". *J. Immunol.*, **77**, 430.
Good, R. A., and Varco, R. L. (1955). "Successful Homograft of Skin in a Child with Agammaglobulinemia". *J. Amer. med. Ass.*, **157**, 713.
— — Aust, J. B., and Zak, S. J. (1957). "Transplantation Studies in Patients with Agammaglobulinemia". *Ann. N.Y. Acad. Sci.*, **64**, 882.
Goodman, M., Greanspon, S. A., and Krakower, C. A. (1955). "The Antigenic Composition of the Various Anatomic Structures of the Canine Kidney". *J. Immunol.*, **76**, 96.
Gordon, L. A., and Richards, V. (1957). "The Use of Homotransplants in the Therapy of Uraemia". *Surgery*, **43**, 163.
Gorer, P. A. (1956) "Some Recent Work on Tumor Immunity". In *Advances in Cancer Research*. Vol. 4. New York: Academic Press.
— and Boyse, E. A. (1959). "Pathological Changes in F_1 Hybrid Mice Following Transplantation of Spleen Cells from Donors of the Parental Strains". *Immunology*, **2**, 182.
Grabar, P., Courcon, J., Merrill, J. P., Ilberry, P. L. T., and Loutit, J. F. (1958). "Immunoelectrophoretic Study of the Serum of Mice Irradiated by Lethal Dose of X-ray and Protected by Rat Bone Marrow". *Transpl. Bull.*, **5**, 58.
Hamburger, J., Vaysse, J., Crosnier, J., Inbiana, M., Lalanne, C. M., Antoine, B., Auvert, J., Soulier, J. P., Dormont, J., Salmon, C. L., Maisonnet, M., and Amiel, J. L. (1959). "Transplantation d'un rein entre jumeaux non monozygotes après irradiation du receveur". *Pr. med.*, **67**, 1773.
Halsted, W. S. (1909). "Auto- and Iso-transplantation, in Dogs, of the Parathyroid Glandules". *J. exp. Med.*, **11**, 175.
Hardin, C. A., and Werder, A. A. (1954). "The Effect of Total Body Irradiation on the Survival of Homologous Skin Grafts on CFW Mice". *Plast. reconstr. Surg.*, **13**, 40.
Hildeman, W. H., and Medawar, P. B. (1959). "Relationship Between Skin Transplantation Immunity and the Formation of Humoral Iso-antibodies in Mice". *Immunology*, **2**, 44.
Hill, A. G. S., and Cruickshank, R. (1953). "A Study of Antigenic Components of Kidney Tissue". *Brit. J. exp. Path.*, **34**, 27.
Hubay, C. A., and Persky, L. (1957). "Properdin and Renal Homografts". *Transpl. Bull.*, **4**, 58.
Hume, D. M., and Egdahl, R. H. (1955). "Progressive Destruction of Renal Homografts Isolated from the Regional Lymphatics of the Host". *Surgery*, **38**, 194.
— Merrill, J., and Miller, B. (1955). "Homologous Transplantation of the Human Kidney". *J. clin. Invest.*, **4**, 327.
Humphries, A. L. (1956). "Renal Homotransplantation in Goats". *Transpl. Bull.*, **3**, 150.
Jordan, G. L., Foster, R. P., and Curd, G. W. (1958). "The Treatment of Hypoparathyroidism by Homotransplantation". *Transpl. Bull.*, **5**, 49.
— — and Gyorkey, F. (1958). "Transplantation of Parathyroid Glands". *Ibid.*, **5**, 392.
Kaliss, N. (1957). "The Survival of Homografts in Mice Pretreated with Antisera to Mouse Tissue". *Ann. N.Y. Acad. Sci.*, **64**, 977.
— (1958). "Immunological Enhancement of Tumor Homografts in Mice". *Cancer Res.*, **18**, 992.
Kamrin, B. B. (1959). "Successful Skin Homografts in Mature Non-littermate Rats Treated with Fractions Containing Alpha-globulins". *Proc. Soc. exp. Biol. N.Y.*, **100**, 58.
Kaplan, H. S., and Smithers, D. W. (1959). "Auto-immunity in Man and Homologous Disease in Mice in Relation to the Malignant Lymphomas". *Lancet*, **2**, 1.
Kelly, W. D., Good, R. A., and Varco, R. L. (1958). "Anergy and Skin Homograft Survival in Hodgkin's Disease". *Surg. Gynec. Obstet.*, **107**, 565.

Dempster, W. J. (1955b). "A consideration of the Cause of Functional Arrest of Homostransplanted Kidneys". *Brit. J. Urol.*, **27**, 66.
— (1957). *An Introduction to Experimental Surgical Studies.* Oxford: Blackwell.
— and Doniach, I. (1954). "Survival of Thyroid Grafts in Relation to Thyroxin Deficiency". *Arch. int. Pharmacodyn.*, **101**, 398.
— and Joekes, A. M. (1952). " Functional Studies of the Kidney Autotransplanted to the Neck of Dogs". *Acta med. scand.*, **147**, 99.
— — (1955). "Emotional Antidiuresis in the Autotransplanted Kidney". *J. Physiol.* **128**, 122.
— Eggleton, M. S., and Shuster, G. (1956). "The Effect of Hypertonic Infusions on Glomerular Filtration Rate and Glucose Reabsorption in the Kidney of the Dog". *Ibid.*, **132**, 213.
— Joekes, A. M., and Oeconomos, N. (1955). "The Function of Kidneys Autotransplanted to the Iliac Vessels". *Ann. R. Coll. Surg. Engl.*, **16**, 324.
— Lennox, B., and Boag, J. W. (1950). "Prolongation of Survival of Skin Homotransplants in the Rabbit by Irradiation of the Host". *Brit. J. exp. Path.*, **31**, 670.
Dukes, C. D., and Blocker, T. G. (1952). "Studies on the Survival of Skin Homografts. 1. Prolongation of Life of Full-thickness Grafts by the Action of Streptokinase-streptodornase". *Ann. Surg.*, **136**, 999.
Dunham, L. J., and Stewart, L. S. (1952–53). "A Survey of Transplantable and Transmissible Animal Tunours". *J. Nat. Cancer Inst.*, **13**, 1299.
Egdahl, R. H., and Hume, D. M. (1956). "Immunologic Studies in Renal Homotransplantation". *Surg. Gynec. Obstet.*, **102**, 450.
— Good, R. A., and Varco, R. L. (1957). "Studies in Homograft and Heterograft Survival". *Surgery*, **42**, 228.
— Roller, F. D., and Varco, R. C. (1957). "Survival and Function of Adrenal Cortex and Skin in Millipore Chambers". *Transpl. Bull.*, **4**, 146.
Eichwald, E. J., and Silmser, C. R. (1955). "The Genetics of Skin Grafting". *Transpl. Bull.*, **2**, 148.
Fagraeus, A. (1948). "Antibody Production in Relation to the Development of Plasma Cells". *Acta med. scand. Suppl.*, 204.
Favour, C. B., Murray, J. E., Wemyss, C. T., Colodny, A., and Miller, B. F. (1953). "Serum Complement Levels in Dogs Undergoing Kidney Homotransplantation." *Proc. Soc. exp. Biol. N.Y.*, **83**, 352.
Feldman, M., and Yaffe, D. (1958). "Immunogenetic Studies on X-irradiated Mice Treated with Homologous Hematopoietic Cells". *J. Nat. Cancer Inst.*, **21**, 697.
Felton, L. D. (1949). "The Significance of Antigen in Normal Tissues". *J. Immunol.*, **61**, 107.
Ferrebee, J. W., Lochte, H. L., Jaretzski, A., Sahler, O. D., and Thomas, E. D. (1958). "Successful Marrow Homograft in the Dog after Radiation". *Surgery*, **43**, 576.
— Atkins, L., Lochte, H. L., McFarland, R. B., Jones, A. R., Dammin, G. J., and Thomas, E. D. (1959). "The Collection, Storage and Preparation of Viable Cadaver Marrow for Intravenous Use". *Blood*, **14**, 140.
Fisher, B., Axelrod, A. E., Fisher, E. R., Lee, S. H., and Calvanese, N. (1958). "The Favourable Effect of Pyridoxine Deficiency on Skin Homograft Survival". *Surgery*, **44**, 149.
Fisher, E. R., and Fisher, B. (1959). "Investigation of Rejection of Canine Homotransplants by Fluorescent Antibody Technique". *Proc. Soc. exp. Biol. N.Y.*, **101**. 259.
Freund, J., Thompson, G. E., and Lipton, M. M. (1955). "Aspermatogenesis, Anaphylaxis and Cutaneous Sensitization Induced in the Guinea-pig by Homologous Testicular Extract". *J. exp. Med.*, **101**, 591.
Gammeltoft, A., Neimann Sorensen, A., and Simonsen, M. (1955). "The Acquired Immunity Concept in Kidney Homotransplantation". *Ann. N.Y. Acad. Sci.*, **59**, 448.

Murray, J. E., Merrill, J. P., and Harrison, J. H. (1958). "Kidney Transplantation Between Pairs of Identical Twins." *Ann. Surg.*, **148**, 343.

— Lang, S., Miller, B. F., and Dammin, G. J. (1956). "Prolonged Functional Survival of Renal Autotransplants in the Dog". *Surg. Gynec. Obstet.*, **103**, 15.

— Merrill, J. P., Dammin, G. J., Dealy, J. B., Walter, C. W., Brooke, M. S., and Wilson, R. E. (1960). "Study on Transplantation Immunity After Total Body Irradiations: Clinical and Experimental Investigation". *Surgery*, **48**, 272.

Nathan, P., and Miller, B. F. (1958). "The Histamine Content of Transplanted and Normal Kidneys". *Transpl. Bull.*, **5**, 402.

Nisonoff, A., and Pressman, D. (1959). "Effect of Urea on the Combining Site of an Antibody". *Arch. Biochem.*, **80**, 464.

Nossal, G. J. V. (1959). "Antibody Production by Single Cells. iii. The Histology of Antibody Production". *Brit. J. exp. Path.*, **40**, 301.

Oakley, C. L. (1959). "The Localization of Antibody Production". In *Modern Trends in Pathology*. London: Butterworth.

Oeconomos, N., Hamburger, J., Delinotte, P., Vaysse, J., Richet, G., Antoine, B., Elmelik, E., and Perrin, C. (1953). "Tentative d'homogrereffe nale (rein material) apres nephrectomie pour traumatisone d'un rein unique". *Mem. Acad. Chir.*, **25**, 642.

Owen, R. D. (1945). "Immunogenetic Consequences of Vascular Anastomoses Between Bovine Twins". *Science*, **102**, 400.

Porter, K. A. (1957). "Use of the Sex Difference in Morphology of Polymorphonuclear Leucocytes to Indicate Survival of Marrow Homotransplants". *Transpl. Bull.*, **4**, 129.

Prehn, R. T., Weaver, J. M., and Algire, G. H. (1956). "The Diffusion Chamber Technique Applied to a Study of the Nature of Homograft Resistance". *J. Nat. Cancer Inst.*, **15**, 509.

Puza, A., and Gombos, A. (1958). "Acquired Tolerance of Skin Homografts in Dogs". *Transpl. Bull.*, **5**, 30.

Rogers, B. O., Converse, J. M., Taylor, A. C., and Campbell, R. M. (1953). "The Eosinophile in Skin Homografting". *Proc. Soc. exp. Biol. N.Y.*, **82**, 523.

Schier, W. W., Roth, A., Ostroff, G., and Scheift, M. A. (1956). "Hodgkin's Disease and Immunity". *Amer. J. Med.*, **20**, 94.

Schinkel, P. G., and Ferguson, K. A. (1953). "Skin Transplantation in the Foetal Lamb". *Aust. J. Biol. Sci.*, **6**, 533.

Scothorne, J. R., and McGregor, I. A. (1953). "The Vascularization of Autografts and Homografts of Rabbit Skin". *J. Anat., Lond.*, **87**, 379.

Shambaugh, P. (1936). "Autotransplantation of Parathyroid Glands in the Dog". *Arch. Surg.*, **32**, 709.

Simonsen, M. (1953). "Biological Incompatibility in Kidney Transplantation in Dogs". *Acta path. microbiol. scand.*, **32**, 36.

— (1955). "The Acquired Immunity Concept in Kidney Homotransplantation". *Ann. N.Y. Acad. Sci.*, **59**, 448.

— (1957). "The Impact on the Developing Embryo and Newborn Animal of Adult Homologous Cells". *Acta path. microbiol. scand.*, **90**, 480.

— Buemann, J., Gammeltoft, A., Jensen, F., and Jørgensen, J. (1953). "Biological Incompatibility in Kidney Transplantation in Dogs. 1. Experimental and Morphological Investigations". *Ibid.*, **32**, 1.

Stoerk, H. C., and Eisen, H. N. (1946). "Suppression of Circulating Antibodies in Pyridoxine Deficiency". *Proc. Soc. exp. Biol. N.Y.*, **62**, 88.

Talmadge, D. W., Dixon, F. J., Bukantz, S. C., and Dammin, G. I. (1951). "Antigen Elimination from the Blood as an Early Manifestation of the Immune Response". *J. Immunol.*, **67**, 243.

Thal, A. P., Murray, M. J., and Egne, W. (1959). "Iso-antibody Formation in Chronic Pancreatic Disease". *Lancet*, **2**, 1128.

Trentin, J. J. (1956). "Mortality and Skin Transplantibility in X-irradiated Mice Receiving Isologous, Homologous or Heterologous Bone Marrow". *Proc. Soc. exp. Biol. N.Y.*, **92**, 688.

Kuss, R., Legrain, M., Mathé, G., Nedey, R., Tubiana, M., Lalanne, C. M., Camey, M., Larrieu, M. J., Schwarzenberg, L., Vourc'h, C., Desarmenien, J., Maisonnet, M., and Atallah, F. (1960). "Prémices d'une homo-transplantation renale de soeur à frère non jumeaux après néphrectomie bilatérale et irradiation du receveur". *Pr. méd.*, **68**, 755.
Lampkin, G. H. (1953). "Intolerance of Dizygotic Twin Lambs to Skin Homografts". *Nature, Lond.*, **171**, 975.
Lang, S., Murray, J. E., and Miller, B. F. (1956). "Homotransplantation of Ischaemic Kidneys into Dogs with Experimentally-produced Impairment of Renal Function". *Plast. reconstr. Surg.*, **17**, 211.
Lawrence, H. S. (1959). "Homograft Sensitivity". *Physiol. Rev.*, **39**, 811.
Lehrfeld, J. W., Taylor, A. C., and Converse, J. M. (1954). "Relation of Survival Time to Implantation Time of a Second Set Skin Homografts in the Rat". *Proc. Soc. exp. Biol. N.Y.*, **86**, 849.
Lennox, B., Dempster, W. J., and Boag, J. W. (1952). "Suppression of the Tuberculin Reaction in Rabbits by Total Body Irradiation with X-rays". *Brit. J. exp. Path.*, **33**, 380.
Levinson, M. E., and Necheles, H. (1956). "Successful Prolongation of Survival of Homotransplants of Skin in the Rat". *Plast. reconstr. Surg.*, **17**, 218.
Main, J. M., and Prehn, R. T. (1955). "Successful Skin Homografts After the Administration of High Dosage X-radiation and Homologous Bone Marrow". *J. Nat. Cancer Inst.*, **15**, 1023.
Makinodan, T. (1957). "Immunology of Bone Marrow Transplantation". *J. cell. comp. Physiol.*, **50**, 327.
Mannick, J. A., Lochte, H. L., Ashley, C. A., Thomas, E. D., and Ferrebee, J. W. (1959). "A Functioning Kidney Homotransplant in the Dog". *Surgery*, **46**, 821.
Marino, H., and Benaim, F. (1958). "Experimental Skin Homografts. Effect of Homohemotherapy on their Survival Time". *Amer. J. Surg.*, **95**, 267.
Mathé, G., Jammet, H., Pendie, B., Schwarzenberg, L., Duplan, J. F., Manpin, B., Latarjet, R., Larrier, M. J., Kalic, D., and Djukic, Z. (1959). "Transfusions et greffes de moelle osseuse homoloque chez des humains irradies a haute dose accidentellement". *Rev. fran. clin. biol.*, **4**, 226.
McIndoe, A., and Franceschetti, A. (1950). "Reciprocal Skin Homografts in a Medicolegal Case of Familial Identification of Exchanged Identical Twins". *Brit. J. plast. Surg.*, **2**, 283.
Medawar, P. B. (1944). "The Behaviour and Fate of Skin Autografts and Skin Homografts in Rabbits". *J. Anat., Lond.*, **78**, 176.
— (1958a). "The Immunology of Transplantation". *The Harvey Lectures* 1956–57. New York: Academic Press.
— (1958b). "The Homograft Reaction". *Proc. roy. Soc., B.*, **148**, 145.
Mellors, R. C., and Ortega, L. G. (1956). "New Observations on the Pathogenesis of Glomerulonephritis, Lipid Nephrosis, Periarteritis Nodosa, and Secondary Amyloidosis in Man". *Amer. J. Path.*, **32**, 455.
Michon, L., Hamburger, J., Oeconomos, N., Delinotte, P., Richet, G., Vaysse, J., and Antoine, B. (1953). "Une tentative de transplantation renale chez l'homme". *Pr. med.*, **70**, 1419.
Mitchison, N. A. (1956). "The Colonisation of Irradiated Tissue by Transplanted Spleen Cells". *Brit. J. exp.Path.*, **37**, 239.
— and Dube, O. L. (1955). "Studies on the Immunological Response to Foreign Tumor Transplants in the Mouse. II. The Relation Between Hemagglutinating Antibody and Graft Resistance in the Normal Mouse and Mice Pretreated with Tissue Preparations". *J. exp. Med.*, **102**, 179.
Muirhead, E. E., and Groves, M. (1955). "Homogenous Renal Transplantation in Dogs". *Arch. Path.*, **59**, 223.
— Striman, J. A., Lesch, W., and Jones, F. (1956). "The Reduction of Post-nephrectomy Hypertension by Renal Homotransplantation". *Surg. Gynec. Obstet.*, **103**, 673.

microscopy at ×900 magnification; the accuracy of prediction was about 90 per cent. Differential cell counts were performed on Leishmann-stained smears from the popliteal nodes of 19 immunized and two normal animals. After primary immunization, there was an increased proportion of plasma cells. Plasmoblasts appeared and reached their peak concentration of 16 per thousand on the fifth day. Immature and mature plasma cells were most numerous on the seventh day. After secondary immunization, the response occurred earlier and was greater, blast cells increasing significantly in the first five days. Plasmoblasts seen on the second day reached their peak of 54 per thousand on the fourth day; mature plasma cells were greatest on the sixth day. Antibody production by single cells of every type was determined in microdroplets, five bacteria only being introduced for the test. Of 268 single cells, studied *in vitro*, from primarily stimulated and 385 from secondarily stimulated, animals, 601 could be classified histologically. Of these, 93 formed detectable amounts of antibody; 91 were plasmoblasts or plasma cells. Cells of the plasma series, therefore, seem to be the sole or chief producers of antibody. The amount of antibody produced by individual cells varied widely but was generally higher in the secondary response.

Physiological response of the small bowel to ischaemia

Animal experimentation

LILLIEHEI, GOOTT and MILLER (1959) described the physiological response of the small bowel of the dog to ischaemia, including prolonged *in vitro* preservation of the bowel with successful replacement and survival. Serial determination of the plasma volume, haematocrit and plasma haemoglobin were made before, during and after experiments as sensitive indicators of intestinal ischaemia. The first group of 10 adult mongrel dogs received intramuscular morphine sulphate after fasting for 18 hours. Under phenobarbital anaesthesia the superior mesenteric artery was clamped near its aortic origin. After 3 hours in 5 dogs and 3·5 hours in the other 5, the clamp was removed; in 10 dogs it was not released for 5 hours. Another 5 dogs (group III) were given oral sulphasuxidine, neomycin and milk of magnesia daily for 5 days. On the sixth day the superior mesenteric artery was occluded for 5 hours. In groups IV and V (20 dogs) all collateral vessels to the small bowel were additionally occluded, and in 5 dogs the superior mesenteric artery was clamped for 3 hours; in another 5, for 3·5 hours. In the remaining 10 dogs, in which all collaterals were divided, the superior mesenteric artery was occluded for only 2 hours and the bowel allowed to cool to room temperature (25°–28°C.) The effect of hypothermia was tested in 10 dogs (group VI). After isolation of the superior mesenteric vessels, the collateral blood supply was divided, leaving only the superior mesenteric vessels to supply the bowel. These were then clamped and cannulated. In a few minutes the bowel temperature had dropped to below 10°C. Most dogs tolerated clamping of the superior mesenteric artery alone up to 3·5 hours. When the collateral circulation was also occluded, all but one died. The majority survived a 2-hour circulatory interruption with the bowel cooled to room temperature. When cooled to below 10°C. a 5-hour occlusion was well tolerated. The results in this group show that profound hypothermia (5°C.) of the bowel gives significant protection against total circulatory arrest. An experiment was therefore undertaken to remove the small bowel from the peritoneal cavity and return it as an autograft or homograft after varying periods *in vitro*. In one group of dogs, the removed bowel was placed in a sterile towel for 2 or 3 hours and then returned. In another, it was put in a sterile plastic bag, immersed in saline solution at 5°C. and refrigerated: after 5 hours it was replaced. Ten experiments were done in which the bowel was held *in vitro* up to 2 hours before replacement and 10 in which it was cooled to 5°C. and replaced at 4–5 hours. In the first group, all but 3 dogs survived; in the second, only 2 survived. In every case, however, the bowel retained its viability. Furthermore, survival of many of the dogs for weeks or months indicated that the bowel could survive complete severance of all connexions with the central nervous and lymphatic systems and that anastomoses of the superior mesenteric vessels would remain open. Homografts made in 2 dogs by switching the small bowel of one to the other, have lasted up to 7 days.

Uphoff, D. E. (1957). "Genetic Factors Influencing Protection by Bone Marrow. I. The F_1 Hybrid Effect". *J. Nat. Cancer Inst.*, **19**, 123.
— and Law, L. W. (1958). "Genetic Factors Influencing Irradiation Protection by Bone Marrow. II. The Histocompatibility-2(H-2) locus". *Ibid.*, **20**, 617.
Werder, A. A., and Hardin, C. A. (1954). "The Effect of Splenectomy on the Survival Rate of Homologous Skin Grafts in CFW Mice". *Surgery*, **35**, 405.
Woodruff, M. F. A., and Forman, B. (1950). "Evidence for the Production of Circulating Antibodies by Homografts of Lymphoid Tissue and Skin". *Brit. J. exp. Path.*, **31**, 306.
— and Simpson, L. O. (1955). "Induction of Tolerance to Skin Homografts in Rats by Injection of Cells from the Prospective Donor Soon After Birth". *Ibid.*, 36, 494.

SELECTED ABSTRACTS

"Life without blood"

Boerema and his colleagues (1959) described blood-exchange experiments which were performed on young pigs in a hyperpressure tank. Blood was replaced by plasma or macrodex until the level of haemoglobin was 0·4 per cent. At normal atmospheric pressure this level was not compatible with life. At a pressure of three atmospheres, however, the animals survived for 15 minutes. Transport of physically dissolved oxygen to the cardiac wall was sufficient to enable the heart to maintain its normal action. Electrocardiograms showed no pathological changes and both the circulation and blood pressure remained normal. As artificial respiration was employed throughout the experiments pulmonary oedema seldom occurred. Either the chemical composition of macrodex or the speed of re-infusion may have exerted an influence upon the development of oedema. After the pronounced reduction in the amount of haemoglobin a decrease in the *p*H was recorded. The decrease was attributed to the fact that the blood had lost half its buffering capacity. Breathing oxygen while under inceased pressure, the animals lived for 45 minutes although the level of haemoglobin was not compatible with life at normal pressure. Blood was obtained from normal pigs and infusions were performed until the pre-operative level of haemoglobin was reached. The transfusions proved to be life-saving and recovery was uneventful. In view of their findings the authors conclude that even without hypothermia an animal under a pressure of three atmospheres can remain alive for at least 45 minutes with a haemoglobin level of less than 10 per cent. With no haemoglobin survival can be achieved for 15 minutes. It would seem that, in special circumstances, warm-blooded animals are able to exist without red blood and without biological fluid in the vessels. Among vertebrates, fish belonging to the family *Chaenichthyidae*, have no haemoglobin and no corpuscles, apart from a few leucocytes in the plasma. These fish live in the intensely cold but well aerated deep waters of the fjords of South Georgia. Although the physically dissolved oxygen supplies all requirements the movements of the fish are rather slow. The conditions resemble those imposed during the experiments performed by the authors.

Antibody production by single cells

Histology of antibody production

Nossal (1959) discussed the histology of antibody production. Male Wistar albino rats, fed on mouse pellets and water, were used. The bacteria were *Salmonella adelaide*, flagellar antigens H_1^{fg}; the antigen was a preparation of isolated flagella from *Sal. adelaide*. In lymph nodes removed 1–12 days after primary or secondary immunization, lymphocytes, macrophages, blast cells, polymorphs and the cells of the plasma cell series were distinguished. The last were all larger than lymphocytes with an eccentric nucleus, a perinuclear clear zone and dark blue cytoplasm. Staining of the lymph node cells with orcein light green retained the chief features of cell classification. The histological characteristics of unstained cells were determined by phase contrast

microscopy at ×900 magnification; the accuracy of prediction was about 90 per cent. Differential cell counts were performed on Leishmann-stained smears from the popliteal nodes of 19 immunized and two normal animals. After primary immunization, there was an increased proportion of plasma cells. Plasmoblasts appeared and reached their peak concentration of 16 per thousand on the fifth day. Immature and mature plasma cells were most numerous on the seventh day. After secondary immunization, the response occurred earlier and was greater, blast cells increasing significantly in the first five days. Plasmoblasts seen on the second day reached their peak of 54 per thousand on the fourth day; mature plasma cells were greatest on the sixth day. Antibody production by single cells of every type was determined in microdroplets, five bacteria only being introduced for the test. Of 268 single cells, studied *in vitro*, from primarily stimulated and 385 from secondarily stimulated, animals, 601 could be classified histologically. Of these, 93 formed detectable amounts of antibody; 91 were plasmoblasts or plasma cells. Cells of the plasma series, therefore, seem to be the sole or chief producers of antibody. The amount of antibody produced by individual cells varied widely but was generally higher in the secondary response.

Physiological response of the small bowel to ischaemia

Animal experimentation

Lillehei, Goott and Miller (1959) described the physiological response of the small bowel of the dog to ischaemia, including prolonged *in vitro* preservation of the bowel with successful replacement and survival. Serial determination of the plasma volume, haematocrit and plasma haemoglobin were made before, during and after experiments as sensitive indicators of intestinal ischaemia. The first group of 10 adult mongrel dogs received intramuscular morphine sulphate after fasting for 18 hours. Under phenobarbital anaesthesia the superior mesenteric artery was clamped near its aortic origin. After 3 hours in 5 dogs and 3·5 hours in the other 5, the clamp was removed; in 10 dogs it was not released for 5 hours. Another 5 dogs (group III) were given oral sulphasuxidine, neomycin and milk of magnesia daily for 5 days. On the sixth day the superior mesenteric artery was occluded for 5 hours. In groups IV and V (20 dogs) all collateral vessels to the small bowel were additionally occluded, and in 5 dogs the superior mesenteric artery was clamped for 3 hours; in another 5, for 3·5 hours. In the remaining 10 dogs, in which all collaterals were divided, the superior mesenteric artery was occluded for only 2 hours and the bowel allowed to cool to room temperature (25°–28°C.) The effect of hypothermia was tested in 10 dogs (group VI). After isolation of the superior mesenteric vessels, the collateral blood supply was divided, leaving only the superior mesenteric vessels to supply the bowel. These were then clamped and cannulated. In a few minutes the bowel temperature had dropped to below 10°C. Most dogs tolerated clamping of the superior mesenteric artery alone up to 3·5 hours. When the collateral circulation was also occluded, all but one died. The majority survived a 2-hour circulatory interruption with the bowel cooled to room temperature. When cooled to below 10°C. a 5-hour occlusion was well tolerated. The results in this group show that profound hypothermia (5°C.) of the bowel gives significant protection against total circulatory arrest. An experiment was therefore undertaken to remove the small bowel from the peritoneal cavity and return it as an autograft or homograft after varying periods *in vitro*. In one group of dogs, the removed bowel was placed in a sterile towel for 2 or 3 hours and then returned. In another, it was put in a sterile plastic bag, immersed in saline solution at 5°C. and refrigerated: after 5 hours it was replaced. Ten experiments were done in which the bowel was held *in vitro* up to 2 hours before replacement and 10 in which it was cooled to 5°C. and replaced at 4–5 hours. In the first group, all but 3 dogs survived; in the second, only 2 survived. In every case, however, the bowel retained its viability. Furthermore, survival of many of the dogs for weeks or months indicated that the bowel could survive complete severance of all connexions with the central nervous and lymphatic systems and that anastomoses of the superior mesenteric vessels would remain open. Homografts made in 2 dogs by switching the small bowel of one to the other, have lasted up to 7 days.

Histochemical changes in rat kidney in magnesium deprivation

HESS and his colleagues (1958) reviewed histochemical changes in rat kidney in magnesium deprivation. Magnesium ions are essential in the maintenance of mitochondrial structure and function; the cellular changes resulting from depletion are studied. Young female rats were used; the materials and methods are described. After 3 days of magnesium deprivation, mitochondrial swelling was observed in the kidney tissue, confined at first to the distal segment of the proximal convolution, and closely followed by the appearance of lipid droplets. At 6 days, swelling was seen in segmental parts of collecting ducts near the papillary tip, with patchy swelling in the medullary interstitial cells and the thin limb of Henle's loop. At 9 days, epithelial necrosis and calcification occurred in limited distal segments of the proximal convolutions, with marked decrease in mitochondrial enzymic activity. A close relationship was shown between a decrease of plasma magnesium, increase of plasma calcium and mitochondrial change. From 12 to 20 days, the mitochondrial swelling in the proximal convolutions of the outer cortex became more pronounced. It occurred in a lesser degree in Henle's loop. Calcium deposits were found throughout the inner cortex and occasionally in the necrotic zones of the outer cortex. Visible calcification was accompanied by a marked rise of renal calcium content. From 41 to 50 days, little further damage was seen. Psoas muscle exhibited sarcosomal swelling at 20 days. In the earlier phases mitochondrial swelling was accompanied by significant increase of diaphorase and dehydrogenase activity. The changes observed in the cytoplasm of tubular epithelia suggest that the kidney damage is the result of magnesium deprivation and parallels the early fall in plasma magnesium concentration. It would also appear that in magnesium-deficient animals mitochondria differ markedly in their response to injury in the various kidney segments.

Kidney homotransplant

Functioning transplant in the dog

MANNICK and his colleagues (1959) described a functioning kidney homotransplant in the dog. The work on mice of Lorenz and his colleagues in 1951 and Prenz in 1955 suggested a general method of homotransplantation of tissues and organs in mammals, including man. Theoretically, if a homograft of bone marrow can be accepted, all other tissues from the same donor should be tolerated. A male beagle of 8 months was given total-body irradiation by two cobalt 60 units. Total dosage was 1,300 roentgen in 12 hours Prophylactic penicillin and streptomycin and weekly injections of hyperimmune dog serum were administered. Eight days after irradiation, the dog received a homograft of fresh bone marrow from the femur of an unrelated adult female beagle. During the succeeding week, he was given frequent transfusions of her whole blood and platelets. On the twenty-fourth day a kidney was transplanted. By the tenth day after infusion of homologous marrow, the dog showed haematological evidence of a successful graft. Female *polymorphonuclear leucocytes appeared in the peripheral blood* and the blood platelets rose. The dog began to recover and gained weight. On the thirty-fourth day after irradiation, the dog's own kidneys were removed. A biopsy taken of the renal transplant showed normal kidney tissue. The blood urea nitrogen which rose immediately after nephrectomy, soon fell to normal. After remaining in excellent condition until the sixty-second day, the animal suddenly developed thrombocytopenia with a platelet count of 10,000 per cubic millimetre which later rose to 84,000. Despite cortisone therapy and oral tetracycline, he developed pneumonia on the sixty-eighth day and died, in severe respiratory distress, on the seventy-third day. At necropsy, the homografted kidney appeared normal, and the lungs contained haemorrhagic foci. Microscopically, the lung showed a severe broncho-pneumonia. The lymph nodes revealed lymphocytes; the peribronchial nodes, necrosis and polymorphonuclear leucocyte infiltration. The bone marrow showed a preponderance of myeloid cells and numerous megakaryocytes. The dog's survival was of sufficient duration to demonstrate that an adult animal can accept a homotransplanted kidney for a useful *period of time. Further studies will show whether* such animals will react to grafts of skin or kidney from donors other than the marrow donor.

Mammalian homotransplants of skin

Attempts to induce tolerance

ASHLEY and his colleagues (1959) presented studies on mammalian homotransplants of skin. They have already shown that tolerance may be induced with pooled blood antigens and with certain nuclear and cytoplasmic components. In two experiments, pregnant rats were injected intracardially with ribonucleic acid (RNA) and desoxyribonucleic acid (DNA) in an attempt to cross the placental barrier and induce prolonged tolerance in the offspring. In two additional groups radioactive labelled RNA ^{14}C and DNA ^{14}C were injected to verify the passage of the nuclear and cytoplasmic components across the barrier. Rats of the Long Evans and Wistar strains were used. In the first experiment, 10 rats, 20 days pregnant, were injected with 0·3–0·4 millilitre of RNA from the antigen donor pool, the Long Evans rats receiving RNA from the Wistar and vice versa. The offspring were grafted with skin from animals from the same strain as the RNA donors, at 20, 30, and 40 days. In the second experiment, DNA replaced RNA. In the third experiment, 4 Long Evans rats and 2 Wistar, 16–17 days pregnant, received 0·5 millilitre of radioactive RNA. After 24 hours, the foetuses, maternal liver, spleen and blood sample were taken for analysis of radioactivity. In the fourth experiment ^{14}C labelled DNA replaced radioactive RNA. In the first experiment 18 per cent of the grafts took in the 20-day old rats, representing an 8–9 per cent increase over the controls. Rats grafted at 30 days showed a 6 per cent take; those at 40 days had no appreciable take after 14 days. In the second experiment, the difference between the treated and untreated animals was negligible. In the third and fourth experiments, significant amounts of ^{14}C were found in the foetuses, indicating the passage of the cellular components.

Alveolar gas concentrations in lobe of dog's lung

Effect of bronchial and arterial constriction

WEST and HUGH-JONES (1959) described patterns of gas flow in the upper bronchial tree, a hollow cast of which was made by the method described. The patterns of gas flow were studied indirectly by water and dye and directly by using different gases and sampling with the mass spectrometer. The distribution of gas was examined by passing nitrogen through all but one of the segmental bronchi, argon through the remaining one. Tracheal flow rates were recorded by a wire mesh flow meter. The distribution of expirate for each segmental bronchus was studied by using dye and water at varying flow rates. At low rates, flow was laminar throughout the upper bronchial tree but, as the rate increased, turbulence arose in the trachea and extended to the main and lobar bronchi. Studies with argon and air confirmed this pattern. During inspiration the tracheal flow was laminar up to equivalent flow rates of 10 litres of air per minute. At higher rates, turbulence occurred and extended to the bronchi. Thus, streamline flow in the bronchi was lost at much lower rates on expiration. Measurements were also made in open-chested dogs. Argon was slowly injected into the lateral segmental bronchus of the left lower lobe. The tip of the sampling tube was placed in the left main bronchus and the tube rotated. Definite concentration differences occurred across the bronchus. Similar results were obtained on the right side. At diagnostic bronchoscopy on three patients, the technique was repeated. Rotation of the sampling tube again resulted in different concentrations of argon. Attempts were made to demonstrate the penetration of argon from the left lower lobe into the bronchus of the left upper lobe as was done in the model. Very little argon was sampled early in expiration but later, peaks of 15 per cent were recorded. These had the same frequency as the heart beat. The chief experimental aim was to determine the distribution of flow from the segmental bronchi in order to interpret the results of sampling at bronchoscopy. The failure of the gas from segmental bronchi to mix completely in the lobar or main bronchi, suggested by the model experiments was confirmed in the dogs and normal human beings.

Post-stenotic dilatation

Experimental observations

BRUNS and his colleagues (1959) presented experimental observations on post-stenotic dilatation. Dilatation of a vessel downstream is not uncommon in aortic or pulmonary stenosis or coarctation of the aorta and may occur in a region of relatively low pressure. A review of the factors involved in producing murmurs discounts the classical theory of turbulence. A new theory attributes murmurs to nearly periodic pressure fluctuations in the wake downstream from a constriction. Because of the obstructed blood flow, the fluctuations are not strictly periodic and are of a much greater intensity than could be expected from turbulence. Since the energy produced is concentrated in the region immediately downstream from the obstruction, murmurs should be intensified there. In the same way, the vibrations of a thrill should be maximal just distal to the stenosis. Damage resulting from these vibrations could so affect the vessel wall as to produce structural fatigue and dilatation even in a low-pressure area. Experiments were undertaken to test this hypothesis. Thin-walled latex rubber tubes were filled with water and, held under a static pressure, were subjected to vibration. Hydrostatic load and periodic pressure fluctuation were the only forces applied. After 7–120 hours, a moderate dilatation was noted in the tubing wall subjected to vibration. Five hours later, the stressed segment was unable to withstand the original hydrostatic pressure and progressive dilatation was seen. The higher the static pressure, the earlier was the dilatation. In a further experiment to test the relative effect of the various factors involved in post-stenotic dilatation, short segments of tubing were subjected to differing pressures. Results showed that vibratory stress was the most significant factor. Many theories have been propounded to explain post-stenotic dilatation on physical grounds. Robicsek and his colleagues in 1958, while supporting turbulence, admitted the importance of cavitation in producing dilatation, by injury to the blood vessel wall. Cavitation, however, will not occur in blood unless the driving force is at least 350 mm.Hg., a pressure rarely encountered in the body.

REFERENCES

Ashley, F. L., McNall, E. G., Garcia, E. N., Sloan, R. F., and Edwards, J. W. (1959). *Amer. J. Surg.*, **98**, 217.

Boerema, I., Meyne, N. G., Brummelkamp, W. H., Bouma, S., Mensch, M. H., Kamermans, F., Hanf, M. S., and Van Aalderen, W. (1959). *Arch. Chir. Neerl.*, **11**, 70.

Bruns, D. L., Connelly, J. E., Holman, E., and Stofer, R. C. (1959). *J. Thor. Cardiovasc. Surg.*, **38**, 662.

Hess, R., Macintyre, I., Alcock, N., and Pearse, A. G. E. (1958). *Brit. J. exp. Path.*, **40**, 80.

Lilliehei, R. C., Goott, B., and Miller, F. A. (1959). *Ann. Surg.*, **150**, 543.

Mannick, J. A., Lochte, H. L. Jnr., Ashley, C. A., Thomas, C. D., and Ferrebee, J. W. (1959). *Surgery*, **46**, 821.

Nossal, G. J. V. (1959). *Brit. J. exp. Path.*, **40**, 301.

West, J. D., and Hugh-Jones, P. (1959). *J. app. Phys.*, **14**, 743.

TEMPOROMANDIBULAR DISORDERS

The Result of Trauma, Malocclusion and Muscular Imbalance

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INTRODUCTION

The commonest disorders of the temporomandibular joint are the result of trauma, malocclusion and muscular tension or trismus. The word "arthrosis" is a convenient descriptive term for the group, synonyms for which are Costen's syndrome, disorganization or dysfunction of the joint, and clicking jaw.

There seems to be a clinical state which exists before positive evidence of degeneration or osteoarthritis of the joint can be substantiated; if this is recognized and treated most cases can be cured. Blackwood (1959) and Bauer (1940) described in detail the pathology of the degenerative changes that can take place in the temporomandibular joint, while Bennett (1948) and others claimed that some of these changes in otherwise healthy joints can be seen as early as the second decade of life—from which it can be inferred that even normal functional stresses may lead to damage of the articular cartilage and that some damage to the temporomandibular joint can occur in persons with normal musculature and occlusion; fortunately it does not necessarily follow that all persons with abnormal occlusion or musculature will develop joint symptoms.

The movements, position and stresses of the temporomandibular joint are dependent not only on the musculature and ligaments, but also on the relations of the upper and lower teeth through which the greater part of the load is normally transmitted from the mandible to the skull. It has been traditional to describe the mandible as a lever of the third class and according to a formula by Craddock (1951) the strain on the joint is at least doubled if the crushing force in the act of mastication is moved forward from the molars to the incisor teeth. Sicher (1947) and Robinson (1946) have shown that the inner structure of the temporomandibular joint is not that which is usually associated with stress-bearing joints.

The substance of Mr. Hankey's contribution was communicated to the Section of Physical Medicine of the Royal Society of Medicine and was published in the *Proceedings* (49,983) It is reproduced here by courtesy of the Honorary Editors of the *Proceedings of the Royal Society of Medicine*. Figures 63-65, 68, 69, 71, 74-76 also accompanied that article.

Robinson suggested the theory of a non-lever action of the mandible, and the electromyographic analysis of the muscles of mastication by Moyers (1950) supported this. According to Moyers, the direction of the muscle pull, the sequence of contractions and the action of synergists all show that the resultant force is in the denture and that there can be no lever action when the resistance is directly in line with the resultant of the applied force. Tulley (1957) has summarized much of the electromyographic work which has been done on the muscles of mastication and considered muscle spasm to be an important factor in the production of pain.

The teeth and their supporting structures should bear the heavy stresses for which they are designed and the joint should normally be free of heavy strain. It follows that any deviation from the normal in occlusion or muscular physiology, which may upset the nice balance as between the two joints of the mandible and the skull, may have a damaging influence on the articular components. This has, in many instances, been found to be the case and the success of conservative treatment has been achieved by restoring that equilibrium as nearly as possible.

A detailed description of the anatomy and histology of the temporomandibular joint and of the muscles of mastication can be found in the publications of Sicher (1952), Shapiro (1947), Sarnat (1951) and others.

ANATOMY AND HISTOLOGY

Temporomandibular joint

The temporomandibular joint is "the articulation between the mandible and the cranium. It is a highly specialized joint and distinguished from most others by the fact that the articulating surfaces are *not* covered by hyaline cartilage but by an avascular fibrous tissue which only sometimes contains a few cartilage cells. The movements of the mandible are restricted because of its bilateral articulation with the cranium so that the right and left joints are coupled together. It is a complex joint because a disc or meniscus is interposed between the temporal bone and the mandibular condyle, dividing the articular space into upper and lower compartments; in the upper compartment gliding or translatory movements of the meniscus on the temporal bone take place, while in the lower compartment there is an eccentric hinge movement of the condylar head in relation to the meniscus. The temporomandibular joint can best be described as a hinge joint with a movable socket" (Sicher, 1951).

A photomicrograph of a sagittal section of the joint of a child aged 3 years (Fig. 63) shows the outline of the joint cavities, the disc in between the condyle and the eminentia, the muscle fibres attached to the anterior ridge of the disc, the thin intermediate or central portion of the disc and the thick posterior ridge or dome of the disc fitting up into the glenoid fossa. The disc behind splits into two layers; a thick upper layer of loose vascular and elastic tissue attached to the posterior margin of the temporal bone and blending with the posterior capsular fibres, and a thin lower layer of dense collagenous fibres, similar to the main body of the disc, continued downwards behind and attached to the neck of the condyle. The articular surfaces of the condyle and eminentia are covered with a layer of fibrous tissue which is not continued up into the depth of the fossa, where the bone separating the joint from the brain is thin and not meant to resist pressure. The growth centre of

the condylar head is a thin layer of hyaline cartilage between the fibrous covering and the bone; after normal cessation of growth this cartilage still persists, but in a gradually decreasing amount, and is of importance for the explanation of certain growth anomalies.



Fig. 63.—Photomicrograph of a sagittal section through the left temporomandibular joint of a child aged 3 years. Stained haematoxylin and eosin. A: upper joint cavity and glenoid fossa; B: cancellous bone of eminentia; C: posterior thick ridge of disc; D: loose vascular connective and elastic tissue attaching posterior ridge of disc to temporal bone and posterior wall of capsule; *E: lower joint cavity; F: hyaline cartilage—the condylar growth centre;* G: thin collagenous posterior downward prolongation of disc inserted into neck of condyle behind; H: fibrous tissue layer, covering articular surfaces of eminentia and condyle; K: anterior ridge of disc; L: cancellous bone of condyle; M: fibres of lateral pterygoid muscle.

Condyle of the mandible

The condyle of the mandible is about twice as wide medio-laterally as antero-posteriorly. The shape and size relative to that of the glenoid fossa vary in different individuals. The smooth upper convex surface of the head faces upwards and forwards so that in profile the neck seems to be bent forwards. There is usually a transverse ridge at the summit separating a short anterior slope from a longer and more gradual posterior slope (*see* Fig. 66). The axes of the two condyles are not in line facing the front, but form an obtuse angle to one another of about 145 degrees so that lines drawn through each axis and extended medially will cross at the anterior edge of the foramen magnum. There are distinct bony tubercles below the lateral and medial poles for the attachments of the meniscus and capsule.

The ligaments

The important ligaments of the joint are the capsular and the lateral or temporomandibular (Fig. 64); the latter is a dense collagenous thickening of the

former on the lateral side of the joint passing downwards and backwards from the root of the zygoma above to the neck of the condyle below and behind. It is normally taut in all positions of the joint and serves to keep the condyle, disc and temporal bone firmly opposed (Rees, 1954) and to prevent backward displacement of the condyle.

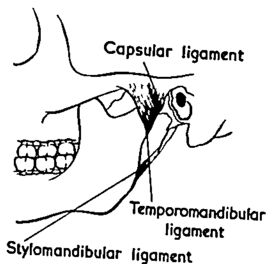


FIG. 64.—Drawing, lateral view, to show the two main ligaments of the temporomandibular joint.

The capsule

The capsule between the margins of the articular surface of the temporal bone and the circumference of the disc is very loose to allow extensive gliding movement in the upper compartment of the joint; in front the fibres are so loose that a dislocation forwards of the condyle can easily occur.

The capsular fibres below the disc are short and tight and are almost immediately inserted into the neck of the condyle, binding and closely conforming the disc to it. An injection into the upper joint space is thus very much easier to accomplish than into the lower. The posterior wall of the capsule (*see* Fig. 66) is inseparably blended with the vascular and elastic posterior attachment of the disc, and its fibres are only distinguished because they run directly downwards from the temporal bone to the neck of the condyle behind. The space between the posterior wall of the capsule and the tympanic plate is occupied by loose areolar tissue and an upper extension of the parotid gland.

The meniscus

The meniscus is composed of interlacing bundles of thick collagen fibres which on the surface run parallel to it. The centre of the disc is bloodless, but the periphery has a good blood and nerve supply, especially from the posterior attachment. It is unlikely that the bloodless centre portion, if torn or perforated, is capable of repair; but it seems probable that an injury or tear of the peripheral attachment to the capsule can heal if rested, thus accounting for the many cases of temporary derangement which recover. Elastic fibres (Hankey, 1954) are present in considerable quantity in the loose upper layer of the posterior attachment of the disc

to the temporal bone and a few can be found in the disc itself of a young person; present also in this layer are nerve fibres and many small vessels.

Nerve supply

The joint is supplied by twigs from the auriculo-temporal branch of the third division of the fifth nerve which enter the capsule from behind; sometimes masseteric twigs also enter laterally. The auriculo-temporal nerve itself lies well below the attachments of the capsule and cannot be compressed against the tympanic plate by a retruded condyle.

Blood supply

Small vessels from the superficial temporal or internal maxillary branches of the external carotid artery enter the capsule behind; the vascularity of the synovium is considerable and profuse bleeding can be troublesome at surgical operation for removal of the disc.

Backward pressure of the condyle on the posterior vascular attachment of the disc, or fibrosis and contraction of the capsule, may impair the vitality of the articulation and at the same time give rise to local or referred pain or reflex muscular spasm. Direct condylar pressure on the chorda tympani as originally claimed by Costen (1934) is, however, well nigh impossible, and when tympanic erosion has been found it has usually been due to the spread of infection from the ear.

Synovial membrane

A synovial membrane as such does not cover the articular surfaces, but in the loose fornices and peripheral boundaries of the joint cavities there is a cellular layer, rich in cells and blood vessels, often thrown into folds or villi. It is from these cells that the synovial fluid is secreted and through this the avascular tissues of the joint receive their nutrition.

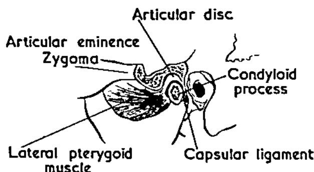


FIG. 65.—Drawing, lateral view, to show the insertion of the fibres of the upper head of the lateral pterygoid muscle into the anterior edge of the disc, while the fibres of the lower head are inserted directly into the anterior surface of the neck of the condyle.

Lateral pterygoid muscle

The lateral pterygoid muscle (Fig. 65) is inserted into the anterior wall of the capsule and anterior edge of the disc by some of the fibres of its upper head. The rest of the muscle is inserted directly into the anterior surface of the neck of the

former on the lateral side of the joint passing downwards and backwards from the root of the zygoma above to the neck of the condyle below and behind. It is normally taut in all positions of the joint and serves to keep the condyle, disc and temporal bone firmly opposed (Rees, 1954) and to prevent backward displacement of the condyle.

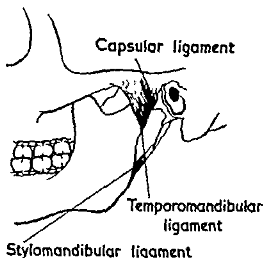


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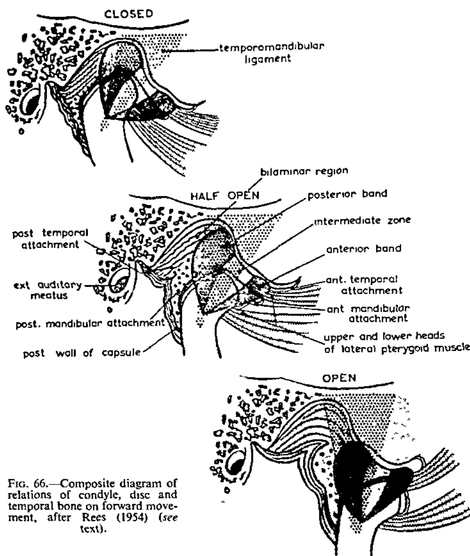


FIG. 66.—Composite diagram of relations of condyle, disc and temporal bone on forward movement, after Rees (1954) (*see* text).

ligament immediately below the disc, is thus able to rotate relative to the disc and a different part of the disc is in contact with the ridge between the anterior and posterior slopes of the head for each position of the mandible; when closed the thick posterior band of the disc filling the depth of the fossa will be in contact; when the mouth is half open, and the condyle is opposite the maximum convexity of the eminentia, the thin middle portion will be in contact; and when the condylar ridge passes below and in front of the eminentia the anterior band will be in contact. The varying thicknesses of the disc allow the condyle to move forward in a simple arc instead of following the sinuous temporal contours.

condyle below the joint. The upper head is thus capable of exerting an antero-medial traction on the disc while the rest of the muscle pulls directly on the mandible; this arrangement serves as a balancing fixation for the disc and prevents it slipping backwards when the jaws are closed forcibly on food between the teeth. According to Rees (1954) a few of the deep fibres of the masseter blend with the antero-lateral aspect of the capsule and meniscus and may thus counteract the medial pull of the pterygoid.

In the positions of rest and normal occlusion (*see* Fig. 67) the head of the condyle is held balanced by the lateral pterygoid against the posterior slope of the eminentia and is not permitted to move back or up into the depth of the glenoid fossa (Thompson, 1949).

Muscle function

The electromyographic conclusions of Moyers (1950) are, very briefly, as follows —the various movements of the mandible are effected by the close interaction or synergia of several muscles at once. Depression, as substantiated by Last (1954), is brought about initially by the synchronous contraction of both lateral pterygoids followed by the digastric and suprahyoid group of muscles. Elevation is achieved by the co-ordinated contraction of the masseter, medial pterygoid and temporal muscles—it should be noted that the direction of the fibres of the masseter and medial pterygoid also assist in simple protrusion and direct the main force against the dentures. Retraction is effected by the middle and posterior fibres of the temporal muscles. Protrusion is achieved by the simultaneous contraction of the lateral and medial pterygoids. Lateral or grinding movements are brought about by the ipsilateral contraction of the temporal muscle and the contralateral contractions of the lateral and medial pterygoids.

One muscle may contract more strongly during any given movement and may be called the prime mover, but the other muscles are guiding at the same time by minor contractions or passivity.

Anything, therefore, that upsets this delicate muscle balance may also result in strain, and initiate symptoms.

The relations of the condyle, disc and temporal bone on forward movement

Based on the work of Rees (1954) the relations of the condyle, disc and temporal bone on forward movement can now be described. He likened the disc to a visor (Fig. 66) hinged by its attachments to either pole at the condylar axis. He found that the excursion of the condylar head relative to the disc in the lower compartment of the joint, from retrusion to protrusion, was about 8 millimetres, but that the total forward excursion of the condylar ridge relative to the temporal bone was at least 15 millimetres. He verified that the disc relative to the temporal bone moved forward at least 7 millimetres in the upper compartment of the joint. The elastic upper layer of the posterior attachment of the disc can permit this amount of forward movement and is also ideally suited to filling in the glenoid cavity when vacated by the condyle. The forward movement of the disc on opening is due to its close attachment to the neck of the condyle, to the pull of the upper head of the lateral pterygoid upon it and to the fact that it is hinged at the condylar axis. The condyle, suspended by the attachment of the temporomandibular

Extrinsic traumas

Extrinsic traumas were more common in males and were direct or axial. A direct blow on the side of the face in the region of the joint or an axial blow on the chin, besides causing injury at the point of impact, can result in synovitis, haemarthrosis, torn ligaments or a fractured condyle.

If the victim can see the blow coming and the teeth are apart at the moment of impact, the lateral pterygoid tenses to take the strain and the fibres of the upper head may dislodge the disc antero-medially in relation to the condyle after tearing the upper posterior attachment of the disc away from the temporal bone, or else may itself tear away from the front of the disc so that the latter tends to drift distally in the joint. An anterior displacement of the disc will cause obstruction to forward gliding of the condyle with limited opening: distal displacement will prevent full retrusion and closure of the teeth on the same side.

The downward pressure and lateral wrenching employed in the extraction of lower molars may strain the joint ligaments, giving immediate pain in the conscious patient with subsequent symptoms of derangement which can be traced to this event. A true anterior dislocation of the condyle from any cause—for example, the use of a Mason's gag or laryngoscope—may result in a ruptured capsular ligament and effusion into the joint, which should certainly be rested after reduction.

Pain in and around the joint, probably accompanied by local swelling, tenderness and restriction of movement are immediate symptoms of all extrinsic traumas. Radiographs should always be taken to exclude a fractured condyle which is sometimes almost symptomless and may otherwise be missed.

Intrinsic traumas

Intrinsic traumas are self inflicted. Sometimes the onset of symptoms in the joint can be clearly connected by the patient with an incident such as yawning, laughing or eating. There is a sudden sharp pain in the joint as if something is nipped—maybe the disc caught momentarily out of place or a synovial fold drawn in and pinched as can happen in the knee-joint. The sharp pain may be followed by the feeling of something in the way preventing full movement; often self-manipulation restores normal function on the first few occasions: but the joint remains stiff and tender for some days indicating a synovitis. If the jaw can be rested at this stage repair will occur; but this should immediately be followed by correction of any occlusal deformity. If neglected, repeated intrinsic traumas set up degenerative changes in the joint with stretching of the capsule, clicking, and loosening of the conformity of the disc to the condyle. The disc, once injured, may be nipped or crushed repeatedly until it becomes misshapen or split and a permanent painful obstruction to movement. Nothing but its removal will then suffice.

In other patients, there will have been, for a varying length of time, a regular or intermittent click on movement, with or without pain, and unconnected in the first place with a special incident until one day the click suddenly stops. It is then found that the mouth can only be partly opened—this is usually described by the patient as "dislocated" or "out"—and that the joint is extremely painful on trying to force it wider; there may, in addition, be considerable muscle spasm which in itself is painful. The inability to open indicates that a misplaced disc is obstructing

The return of the disc on closure is due to its firm attachments to the neck of the condyle at either pole and particularly to the attachment of the dense collagenous lower layer of the bilaminar portion into the neck behind—perhaps assisted by the recoil of the elastic upper layer.

In extreme retrusion or protrusion the condylar ridge may slip with a bump, jump or click beyond the thick posterior or anterior bands of the disc—in protrusion the disc itself is prevented from going further forward by the limited stretch of the temporal attachment behind, and in retrusion is held by the upper head of the lateral pterygoid.

AETIOLOGY, SYMPTOMS AND SIGNS

A detailed analysis of 250 cases out of more than 500 treated (Hankey, 1954, 1956, 1958) is the basis of the following observations. Throughout the percentages given are of the total 250 cases.

Females were affected from three to four times more often than males and the vast majority of all cases developed symptoms between late adolescence and 40 years of age, that is, during the years when the wisdom teeth erupt and the rest of the permanent teeth are in position. Only 14 per cent of the patients were edentulous. Six per cent sought treatment within a few days of the onset of trouble, indicating how few had acute initial symptoms; the majority came for advice after 2–6 months.

Symptoms Related to the Joint

Eighty-two per cent of the patients had symptoms which they could definitely relate to the joint or to mandibular function and could be classified as clicking jaws or joint dysfunction. The advice of a general, orthopaedic or dental surgeon had usually been sought in the first instance. Thirty per cent of the patients had painless clicks; 27 per cent had painful clicks. The remainder had a variety of symptoms, confined to the region of the joint, such as occasional locking at first reducible by self-manipulation but later merging into a permanently restricted opening. This in turn was at first painful with muscle spasm but later the restriction often became painless owing to the formation of fibrous contractions or adhesions. Others complained of recurrent subluxation either primary or in the joint opposite a restricted one.

The type of pain experienced was momentary, sharp stabbing or a dull gnawing ache, aggravated by eating or movement of the mandible; it was located in the joint or ear, or referred down the inferior dental nerve, up the auriculo-temporal nerve or along the side of the maxilla. Stiffness of the joint on waking in the morning was common. Headaches, neckache, lingual pain and difficulty in swallowing were rare and will be dealt with later. Tinnitus and deafness were very rare indeed.

Mode of onset and cause

In 63 per cent of cases the onset was gradual; in the remainder it was sudden. Only 20 per cent could be attributed to definite extrinsic injury; the rest were due to intrinsic causes.

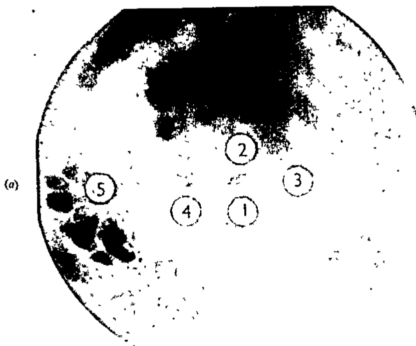




FIG. 67.—Lateral oblique radiographs of the normal temporomandibular joint: (a) closed or at rest; (b) open. 1—head of condyle; 2—glenoid fossa; 3—eminentia; 4—auditory canal; 5—mastoid air cells.

forward movement of the condyle. The good joint then overextends to compensate for the fixed side which may sometimes become painless although still fixed; later still pain begins in the overmobile joint due to capsular stretching, subluxation and muscular imbalance. If the patient is first seen at this stage it may be quite difficult to decide which joint needs the more urgent attention.

The clinical assessment of the range of condylar movement and of the relation of clicks to movement is a most important part of the examination and is well described by Burman and Sinberg (1946). Sometimes symptoms start after relaxation of the jaw in sleep or through lying with the head turned at an acute angle as when prone. Prolonged mouth-opening for conservative dental treatment is very tiring and often causes muscular cramp followed by joint symptoms. The underlying factor in 20 per cent of the cases was an erupting or impacted third molar or carious tooth. A pericoronitis or a painful tooth will necessitate an eccentric bite of accommodation in order to avoid the tender spot; the eccentric bite in turn forces an asymmetrical placing of the condyles in their fossae, with unnatural strains on the muscles and components of the joint.

A singer repeatedly subluxated his left condyle in the effort to reach a higher note; a swimmer strained both joints when streamlining his face to gain more speed; an osculator strained the joints by protruding the tongue too far too often. Such cases can be cured by voluntary self-control.

But the cumulative effect of altered stresses and strains imposed by malocclusion, overclosure or loss of molar support is the most frequent aetiological factor which initiates degenerative changes in the joint.

Twenty-four per cent of the cases had had haphazard extractions (mutilations) with resultant occlusal collapse brought about by the movement, tilting, over-eruption and locking of the remaining teeth: 28 per cent had overclosure of the bite, and half of these were edentulous in one or both jaws: 17 per cent had premature contacts with backward displacement of the condyles; 6 per cent had cross-bites or occlusions locked against lateral grinding; 22 per cent had lack of molar support. Only 3 per cent were completely normal.

It would seem that any of these prolonged and repeated strains sets up changes in the joint and creates a basic weakness; thereafter only a slight injury, of no consequence under normal circumstances, is necessary to start the symptoms of arthrosis.

The aetiology of injury due to malocclusion

The primary function of the mandible is mastication and in the act of crushing of the food the main force is transmitted through the teeth to the maxilla and cranium and only in part to the joints—that is if there is a full dentition in normal occlusion. The normal symmetrically developed mandible, complete with its dentition and musculature, starts all movements of mastication and speech from a position of rest.

The rest position (Thompson, 1949) is fixed by the tonus of the elevator and depressor groups of muscles which, when relaxed, allow the mandible to drop slightly. The teeth are then slightly apart and the space between them, which does not normally measure more than 4 millimetres, is termed the free-way space. If it

light contact. The ability to chew as well as to bite is of great importance and it will be found on trial that many occlusions are locked against lateral grinding. Rectification of this fault alone will relieve tension and ease the strain on many joints.

The teeth of the two jaws can be compared with the teeth of two cogs which are designed to interdigitate exactly: any maladjustment of apposition and the two cogs will wear away where they first hit, or will jam, or will glide into full contact only if the axis of one is adjustable in relation to the other. Radiographs of the joints with the teeth in normal centric occlusion compared with those of the mandible at rest should show very little difference. Any disparity suggests that the cogs or teeth are meeting out of true and that the adjustment has had to be taken up in the joints, imposing an unusual strain upon them.

If certain cusps meet prematurely (Fig. 68) they may act as inclined planes and force the mandible into a lateral deviation or eccentric occlusion: the whole jaw will then be rotated horizontally and radiographs of the joints will show asymmetrically placed condyles—one more deeply placed and retruded in its fossa than the other, which will be normally placed or slightly advanced. Bilateral backward displacement of the mandible and condyles will ensue if there is initial contact of the lower incisors with the palatal surfaces of the uppers—especially when there is a deep overbite with lack of molar growth or support behind (Fig. 69). In radiographs of such a case with the teeth in occlusion both condyles will be retruded in

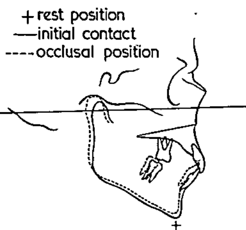


FIG. 69.—Diagram of initial incisal contact with posterior displacement of both condyles on full occlusion (Thompson, 1951).

their fossae as compared with the rest position (Fig. 70). The condyles will be similarly displaced if there is overclosure of the bite with an increased free-way space; this ensues if molar teeth have been extracted and there is lack of molar support, or if the molar occlusion has drifted and collapsed following the extraction of a tooth here and there, or if there has been marked attrition of the occlusal surfaces of the teeth from wear and tear, or if artificial dentures have sunk following the absorption of the alveolus beneath them.

Bruxism or habitual clenching and grinding of the teeth, which takes place often when asleep, may be a sign of emotional stress. With the elevator muscles in an hypertonic state the teeth are gradually worn away by attrition and an overclosure

measures 5 millimetres or more it is said to be increased and there is probable overclosure of the bite. In the position of rest the normal mandible, as judged by the point of the chin, is balanced centrically in midline. If lateral oblique radiographs of the temporomandibular joints are now taken both condyles appear poised half-way up the posterior slopes of the eminentiae, with more joint space above and behind than above and in front (Fig. 67). From the rest position to normal functional occlusion of the teeth the mandible should close centrically by a



FIG. 68.—Radiograph of premature contact of 7| with 7| resulting in posterior displacement of the condyle on the same side.

hinge movement in the lower compartments of the joints without any deviation or gliding (Lindblom, 1953), so that all the teeth meet with equal pressure at one and the same time and, by interlocking of their cusps, prevent further upward and backward movement of the condyles; yet although locked against further retrusion, the cusps should be capable of free lateral grinding movements while remaining in

time the teeth meet in an abnormal occlusion of this type the condyle tends to slip posterior to the disc and the disc becomes progressively looser in its attachment to the head (Fig. 72). A click is heard at the commencement of opening as the head slips over the thick posterior ridge of the disc and re-engages with it, and often a second click is heard towards the end of wide opening as the head slips beyond the anterior ridge of the disc on to the anterior slope of the eminentia. Sooner or later re-engagement fails, the disc remains anterior to the head and locking and pain ensue.

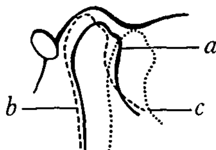


Fig. 71.—Diagram of temporomandibular joint with the condyle in positions of (a) rest, (b) backward and upward displacement in abnormal occlusion, and (c) open mouth.

As a diagnostic point if there is clicking of the joint at the commencement of opening and overclosure is suspected, ask the patient to click and open wide and then to close on to a spatula or the thin flat handle of any instrument placed between the back molars. This will prevent overclosure and on opening again from this new starting point the click is often abolished. In such cases the prognosis of a cure by a bite opening splint or prosthesis is very favourable.

Symptoms Unrelated to the Joint

The group of patients (18 per cent of the cases) who complained only of pain or other sensory changes is now considered. Harris (1937) published an excellent

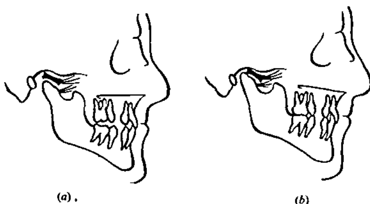


Fig. 72.—Diagram of dislocation of disc in malocclusion. (a) Rest position of disc and condyle in a case of malocclusion with overclosure; (b) probable dislocation of disc when mandibular condyle is forced upward and backward in full occlusion (Thompson, 1951).

of the bite may ensue; but more important, the rest position is almost permanently abolished so that the joints and muscles are always under tension and become painful for this reason alone.



FIG. 70.—Radiograph of a retruded condyle, the result of malocclusion. (Compare with Fig. 67.)

The production of the click

It has been explained that radiographs of the joint will show that the condyle occupies the same position in the glenoid fossa with the teeth in normal centric occlusion as it does with the mandible at rest.

In overclosure, lateral deviation, or backward displacement of the mandible, the condyle may be forced further up and back in the fossa than at rest (Fig. 71). Assuming that the disc is held at the position of rest by its attachment to the condyle and by the pull of the lateral pterygoid muscle, it is reasoned that every

become painful and loose and have to be extracted or, by the agency of the acutely developed proprioceptive sense in the periodontal membrane, the mandible by reflex muscular action moves distally, mesially or eccentrically into a comfortable bite which avoids the painful stimulus. This unnatural action upsets the normal delicate balance between the muscles and may result in spasm and pain without evidence that the joints are as yet affected. Several edentulous patients with obvious overclosure showed no radiographic evidence of condylar retrusion; it is probable that the pain from which they suffered originated in the muscles which were constantly contracting to prevent a displacement which would otherwise have occurred.

Altered sensation or pain in the anterior part of the tongue can be referred from the joint via the lingual nerve.

One patient in particular, an edentulous woman aged 70 years, had been unable to wear her lower full denture for a long time owing to extreme sensitivity and pain of the right anterior two-thirds of the tongue; she had recently only been able to eat the softest of food with great difficulty and was losing weight. The tongue was so tender that she could not tolerate the taking of a lower impression until a right inferior dental and lingual nerve block had been given. She had marked overclosure with condylar retrusion. The lower denture was raised to the correct height with an overlay and before insertion in the mouth a right lingual nerve block with Proctocaine was given which lasted for ten days. She was then able to wear the denture which gave support to her mandible and prevented overclosure. At the end of ten days one more lingual Proctocaine injection was given. From then onwards the pain in the tongue disappeared and she was able to eat in comfort.

Transitory tinnitus or deafness (one per cent) can follow trauma or infection of the medial pterygoid muscle, the reason being that the motor nerve to the tensor tympani and tensor palati muscles is a branch of the nerve to the medial pterygoid. Infection spreading from a wisdom tooth or injury caused by an inferior dental nerve block injection may have this effect.

Pain in the distribution of second and third cervical nerves

So far the areas of pain described have all been within the distribution of the trigeminal nerve and could be referred from one branch to another on the same side. But 5 per cent of the patients had pain up the back of the head and down the side of the neck, reaching as far as the shoulder. This area is within the distribution of the second and third cervical spinal nerves and is more difficult to explain in relation to the joint; the distribution borders on and in some parts, notably the angle of the mandible, overlaps the area of the trigeminal. Stimulation of the second and third cervical nerves can cause not only pain in their sensory distribution but also, through their motor branches, can result in spasm and stiffness of the neck muscles and sternomastoid muscle. The sensory root fibres of the trigeminal nerve concerned with pain, deep pressure and temperature pass down through the pons and medulla as low as the second cervical segment. By synaptic overflow, therefore, the cervical nerves can give rise to referred pain, the point of origin being in the area of the trigeminal.

One case of pain in the throat and on swallowing may well have had a similar neuro-muscular explanation.

A single girl, aged 23 years, a children's nurse, had been off work for nine months complaining of pain down the left sternomastoid muscle and across the midline in the

monograph on the facial neuralgias; one of his conclusions was that the commonest cause of facial pain was of dental origin. More recently the differential diagnosis of facial pain has been dealt with by Stones (1956) and Cohen (1959). Together with all the other possibilities, pain originating from changes in the mechanism of the temporomandibular joint or from imbalance of the muscles of mastication should always be considered.

The patients in this group were unable to relate their symptoms either to the joint or to mandibular function. A higher proportion than usual were male and the average age was over 40 years. They had often consulted a physician, neurologist or otologist in the first instance for earache or some form of cervico-facial neuralgia and, because no definite physical signs could be elicited, might have been diagnosed as suffering from primary trigeminal neuralgia (tic douloureux), migrainous neuralgia or atypical psychogenic facial neuralgia.

Pain of trigeminal distribution

Eleven per cent of the total number of cases complained of more or less continuous neuralgia of varying intensity and depth along the distribution of the second or third divisions of the fifth nerve. Ten per cent complained of pain in and around the ear. On examination, however, the centre from which the pain radiated could often be pin-pointed just anterior to the tragus of the ear and on palpation the temporomandibular joint was more tender than on the normal side. The area of pain distribution can be explained by the fact that the auriculo-temporal branch of the fifth nerve conveys sensation and pain from the anterior and upper part of the external surface of the tympanic membrane and from the anterior half of the external auditory canal, as well as from the joint and the temporal region—it will be remembered that the vagus nerve supplies the remainder of the external surface of the tympanic membrane while the glossopharyngeal nerve supplies its inner side.

Headache up the side of the head was complained of by 6 per cent of the cases, the area of pain roughly corresponding to the distribution of the middle meningeal artery. In the absence of arterial disease or spasm this pain could be referred by the recurrent sensory branch of the third division of the fifth nerve which re-enters the skull with the middle meningeal artery and supplies the same area of dura mater.

In 3 per cent of cases the pain areas corresponded to the origins or insertions of the pterygoid, temporalis or masseter muscles. Campbell (1958), by means of a grid system, plotted the pain patterns of 900 cases and was convinced that in many cases the pain originates in the muscles; he also found that pain centred in areas anterior to the muscles, for instance, infra-orbital or mental, was unfavourable and unlikely to respond to treatment. Muscles in spasm or partial spasm can become painful of themselves although the original cause of the spasm may have been inflammation or trauma. If the meniscus or synovial membrane of the joint is accidentally nipped there is an immediate sharp stab of pain; inflammatory reaction and effusion will be followed by some degree of protective muscle spasm to restrict movement and avoid further pain during healing. Chronic trauma to the joint can therefore exact chronic muscle spasm. If the occlusion is at fault and unequal stresses are exerted upon certain teeth and their supporting structures, then either the teeth are gradually forced into a more comfortable position or they

of an anatomical derangement, psychosomatic precipitation of painful episodes should become impossible. The psychological reaction of the rest of these 100 patients was average and what is to be expected of a patient attending a hospital for medical treatment.

Investigations

In addition to the normal clinical examination, record should be made of the following:

(1) The range of movements of the mandible and the relation of clicks and pain to movement.

(2) The distance between the front teeth with the mouth open.

(3) An estimation of the free-way space.

(4) A chart of the teeth present and their condition.

(5) The type of occlusion.

(6) Radiographs of the joints to show condylar displacement or evidence of arthritis or deformity, and of the teeth to disclose sepsis, impactions, unerupted teeth and so forth. Films of the nasal sinuses will often be wanted as well. Views of both temporomandibular joints should be taken in the closed and wide-open positions; care must be taken that the closed view records the most retrusive molar occlusion possible—patients tend to close on their front teeth, and this gives a faulty protrusive result. An excellent technique for taking these radiographs was given by Craddock (1953). If the normal views suggest arthritis or other pathological change a planograph may be needed to verify.

(7) An analysis of the bite and occlusion after mounting plaster models on an anatomical articulator such as the Dentatus.

Summary

In spite of the great diversity of the clinical picture it is possible to simplify the analysis into three groups, each of which has a dominant presenting feature.

Known acute trauma

In cases of known acute trauma there has been a traumatic incident which can be recalled. Too often such incidents are regarded as trivial and treatment is not given until a state of chronic imbalance and synovitis has arisen. Injury may arise from eating accidents (for instance, cracking a nut, or opening too wide to bite an apple), dental extraction, or the overextension of the mandible during the administration of a general anaesthetic no matter what is the site of the operation.

Recurrent locking, or subluxation

The patient may be unable to link the onset of symptoms with a particular incident. The jaw becomes fixed in the open or closed position. The patient may wake in the morning with the jaw tightly closed, or it may stick open after yawning. Locking may be brief or sustained until a definite muscular or manual effort is made to replace the mandible.

thyroid region, complicated by a feeling of tightness in the throat and difficulty in swallowing. A thorough medical and surgical examination had been negative. After further examination surgeon and dental surgeon both thought the pain was muscular and tensive and that the basic cause of the spasm might be her malocclusion. Most of her teeth were present and in good order but there was a deep overbite and a few of the lower molars were missing; the free-way space was increased. Her occlusion was restored and balanced with a lower plastic overlay, requiring many sittings for careful adjustment and grinding-in of the bite. She became comfortable and relaxed, with relief of all her symptoms, when her bite had been raised six millimetres, and was able to return to work.

It has also been found that the tongue must have ample room for its housing inside the mouth; any constriction of its space will lead to muscular aching and pain at its root and in the throat.

Explanation of symptoms

It will have been realized that many of this group of patients (18 per cent of the total) had a mixture of symptoms. In 7 per cent the occlusal deformity was an edentulous state with overclosure, while the remaining 11 per cent had lack of molar support.

The most likely explanation for the symptoms of this group is either that the pain or other sensory change is reflex or referred from the joint due to the pressure of the retruded condyle upon the nerves and vascular tissues in the posterior part of the glenoid fossa and to the subsequent degenerative changes taking place, or that the pain originates in muscles under constant tension in their endeavour to prevent condylar displacement. Suffice to say that the vast majority of cases of all groups will be cured or relieved by restoring the faulty occlusion to normal.

Costen's syndrome

In 1934 Costen first published an account of his syndrome, symptoms of which were as those just described except that he also emphasized deafness, tinnitus, and changes of taste—symptoms absent in this series. He accounted for these symptoms by the pressure of the retruded condyles in overclosure of the bite upon the chorda tympani, upon the eustachian tube or upon the auriculo-temporal nerve, or even by direct condylar erosion of the roof of the glenoid fossa or of the tympanic plate. These original anatomical explanations have not been substantiated (Zimmerman, 1951) and in the course of years Costen (1956) has had to modify his concepts; he has, however, rendered a great service by publicizing the relationship between malocclusion, temporomandibular joint dysfunction and facial pain.

Psychiatric Assessment

There is still a tendency to dismiss the symptoms of a large proportion of patients complaining of temporomandibular dysfunction or of cervico-facial neuralgia as being of psychoneurotic origin. Yet out of a chance 100 patients (Hankey, 1958) only 3 could be definitely diagnosed as psychoneurotic and 9 more suffered from a mild degree of anxiety neurosis. The pain threshold of many may have been low but their pain was very real. Of the 18 per cent who complained of pain only, without reference to the joint, none was psychopathic. With the physical correction

of an anatomical derangement, psychosomatic precipitation of painful episodes should become impossible. The psychological reaction of the rest of these 100 patients was average and what is to be expected of a patient attending a hospital for medical treatment.

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Referred pain

Referred pain may occur with or without locking or clicking. We have seen a number of cases in which the patient has been aware of a click, but has never associated the derangement of the joint with the symptom pain for which the treatment has been sought. Every case of "trigeminal neuralgia" for which no cause is found should be examined specifically to exclude the temporomandibular joint as an aetiological factor. It cannot be emphasized too strongly that the ramifications of the trigeminal nerve, its connexions with the glossopharyngeal and the vagus nerves, make the possible distribution of pain very wide. This conception is borne out in clinical practice.

TREATMENT

The treatment can best be considered under three main headings: prevention, causative management and operative surgery.

Prevention

A full normal dentition maintained in good order is the best way to prevent temporomandibular arthrosis from developing as the result of intrinsic traumas.

Children

A greatly extended service for the conservation of children's teeth and for orthodontic correction of hereditary malocclusions and immature muscle patterns is needed, especially those abnormalities known as Angle's class 2, where there is a tendency to mandibular retrusion with a deep incisor overbite.

If a deciduous tooth has to be extracted for other than orthodontic reasons, the space into which its successor should erupt must be maintained by an appliance to prevent subsequent irregularity or impaction of the permanent tooth. Similarly if a permanent molar tooth has to be extracted the space should always be maintained by a prosthesis or fixed bridge to prevent movement or tilting of the teeth on each side of the gap and overeruption of the unopposed tooth.

Adults

In the adult the functional occlusion should be kept centric and at the correct level by preventing loss of vertical height from any cause. The weight of partial dentures should always be borne on the teeth, not on the gums, to prevent the dentures from sinking.

Where there is bruxism or natural attrition the occlusal surfaces of the teeth should be protected from wearing away by inlays or an overlaid prosthesis to be worn at night.

Full artificial dentures, even though comfortable, should be checked at regular intervals and kept at the correct height by relining them, in order to compensate for the inevitable sinking and loss of vertical dimension which follows natural alveolar resorption.

The profile of a typical case of overclosure with loss of vertical dimension

(Fig. 73) shows the diminution of the lower third of the face from the lip-line to the point of the chin as compared with the middle third from the lip-line to the pupil of the eye, and with the upper third from the ala nasae to the crest of the eyebrow. In a well-proportioned face these measurements are all equal.



Fig. 73.—Profile of a typical case of overclosure (*see* text).

Causative Treatment

Acute cases

The management of patients with sudden acute pain in the joint is the same whether caused by extrinsic or intrinsic injury. Simple rest by the application of a barrel bandage, with strict adherence to a fluid diet for a few days may be effective, but even when symptoms seem to have abated any malocclusion found at the initial examination should be corrected, or recurrence of symptoms may be expected.

If bandaging does not relieve symptoms, and from the first in cases of great severity with effusion and trismus, interdental wiring is essential and immobilization should be maintained for at least ten days. Before this is done, radiographs are taken and any dislocation or fracture is reduced.

When the symptoms have abated, movement and function must be gradually restored with the aid of local heat and massage followed by muscle exercises carried out in front of a mirror—the aim usually being to strengthen the lateral pterygoid

muscles. If radiographs of the joint with the mouth shut show a markedly retruded condyle, every effort should be made to open the bite 2–3 millimetres by means of a splint between the teeth which will reduce the pressure of backward displacement, before wiring the teeth together. The muscle spasm and pain may be so severe that a general anaesthetic is necessary in order to take impressions of the teeth or to fix the wires. Peri-articular or intra-articular injection of lignocaine 2 per cent, or of hydrocortisone, at this stage may relieve the pain and spasm. Proctocaine 2 per cent will have a more prolonged action. Later, when the symptoms have relaxed, a full analysis of the bite must be made and any abnormality of occlusion restored to normal. Sometimes, even after rest, the meniscus is so badly damaged or displaced, as evidenced by snapping, jamming or continual pain, that its surgical removal becomes necessary.

Chronic cases

The chronic cases include two main groups: (1) those patients with joint dysfunction, and (2) those with cervico-facial neuralgia.

In the patients with joint dysfunction the dominant symptoms roughly in order of progression of severity are clicking, clicking with pain, recurrent locking and partial trismus with pain, and recurrent subluxation. Once the click has started the condition may degenerate into meniscal displacement, jamming, pain and disability. Treatment should therefore be started as soon as the click occurs in order to prevent the development of more serious complications. Everything possible should be done for these cases in the way of conservative and orthodontic measures before operative intervention is contemplated.

In the patients of the second group there is facial neuralgia without reference to the joint and without clinical evidence of joint dysfunction.

The conservative treatment for both groups is the same.

Reflex trismus and muscle spasm

Reflex trismus and muscle spasm can often be traced to the irritation of an erupting, carious or impacted tooth, and is sometimes accompanied by a temporary clicking or derangement of the joint probably due to the attachments of the masseter and lateral pterygoid to the meniscus Removal of the offending tooth often effects a speedy cure.

Overclosure of the bite and initial contact

In overclosure and many Angle's class 2 type of occlusions there is an initial incisor contact because of lack of vertical growth of the alveolus supporting the molar teeth. The free-way space is increased and the mandible is gradually forced backwards to enable the molars to occlude. The condyles on radiological examination will be seen to be tight or retruded in their fossae.

If the molar height can be raised to the level of the initial incisor contact the retrusive condylar displacement will be prevented and the strain on the joints relieved. In children and young adults, the molars can often be induced to erupt further by providing an upper plate upon which the lower incisors bite while the molars are still apart and uncovered; the effect of this method is to reduce

naturally the excessive free-way space. In the adult, where further molar eruption is unlikely, the same effect is achieved by raising the molar contact to the level of the incisor contact by means of a prosthesis or splint which covers the occlusal surfaces of either the upper or the lower molars, or in extreme cases of both.

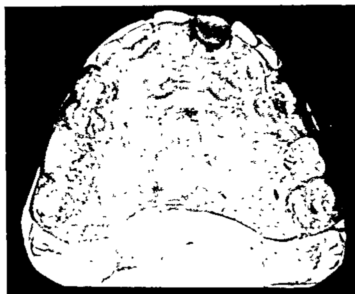


FIG. 74.—A trial upper acrylic overlaid splint.

The trial splint (Fig. 74) in the first place is always made of clear acrylic for ease of adjustment; many adjustments by careful grinding have to be made until the optimum and most comfortable occlusion has been achieved. Relief of tension and other symptoms will follow. Later the trial splint can be replaced by a much less bulky and more comfortable permanent appliance (Fig. 75) in gold or chrome-cobalt



FIG. 75.—A permanent upper gold and acrylic overlaid prosthesis.

alloy. With the flat balanced occlusion provided by the appliance the mandible, no longer influenced by intervening cusps, is enabled to assume its natural centric relation to the maxilla and the displaced condyles resume their normal position in occlusion. The same procedure is followed where the malocclusion is the result of attrition or loss of molar teeth.

In edentulous patients, already wearing full dentures, the excessive free-way space is first reduced by adding a clear acrylic overlay to the lower denture and adjusting until comfortable. Later new dentures must be made to the corrected occlusion.

Premature contact

In premature contact one or several cusps are meeting before the mandible has closed through the normal range of free-way space from rest to occlusion. Careful study of models set up on a fully adjustable anatomical articulator such as the Dentatus will disclose the points of interference which deflect the mandible off centric occlusion and result in condylar displacement.

Selective grinding of these points in the mouth will often be sufficient to restore centric occlusion and cure the arthrosis. Sometimes an obstructing tooth will have to be extracted or the crown cut off and replaced by an artificial crown in correct occlusion; in others the offending tooth can be moved by an orthodontic appliance.

Equilibration

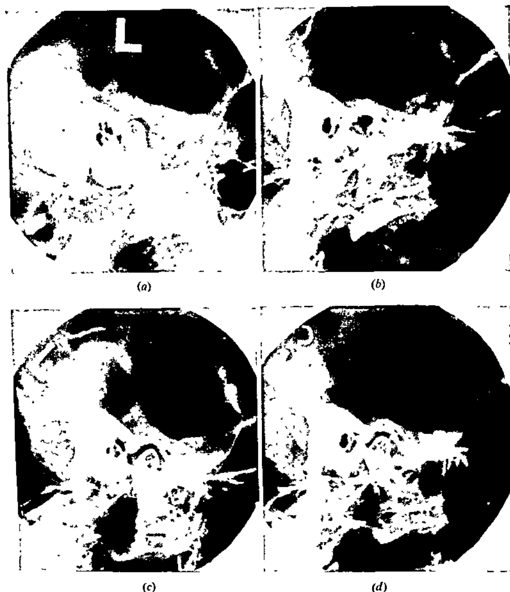
In all cases of malocclusion the aim is to restore the occlusion to the normal centric level and to maintain it in equilibrium so that the teeth can bite equally on both sides and can grind freely in all directions without locking, bumping or unequal muscle strains. At the same time the condyles, which on radiological examination (Fig. 76) before treatment, were seen to be retruded in their fossae when the teeth met in full occlusion, must be retained in their normal resting positions when the teeth occlude naturally or on the appliance. The appliance must never occupy the whole free-way space or intolerable muscle cramps and tender teeth will follow. The thickness of the overlay in the first instance will not often exceed 2–3 millimetres but it may have to be added to more than once before final comfort is achieved.

Physiotherapy

In the form of heat or short-wave diathermy physiotherapy is soothing and of great assistance in many cases of painful or stiff joints. The patient feels that something active is being done and therefore gains confidence; the threshold of pain is correspondingly raised. But short-wave diathermy is contra-indicated when the teeth are wired together. The heat should be followed by deliberate muscle exercises carried out in front of a mirror to strengthen the lateral pterygoid, especially when there has been spasm of the retrusive horizontal fibres of the temporalis. In a few cases training flanges attached to metal cap splints cemented on to the teeth, as in the treatment for fractured condyles, may be employed to rehabilitate muscles where there is a marked deviation of the mandible to one side on opening.

Injections into the joint

Injections of hydrocortisone into the joint cavities have proved of great benefit in patients whose pain was not responding to bite rehabilitation or in whom there was an established osteoarthritis. Its action is somewhat empirical, but like



(*a*) (*b*)

(*c*) (*d*)

FIG. 76—Radiographs of temporomandibular joint before and after correction of backward displacement of the condyle in malocclusion: (*a*) closed, the condyle is retropositioned in the fossa; (*b*) open, there is limited forward movement of the condyle; (*c*) resting, compare with (*a*); normally the condyle does not move back from the resting position; (*d*) closed, biting on overlaid appliance. The condylar position corrected to that of (*c*).

short-wave diathermy it encourages the patient. It should only be tried as an adjunct to basic dental treatment and in its effect has replaced hyaluronidase. The actual intra-articular injection of 1 millilitre of hydrocortisone is quite simple and painless if preceded by a superficial and peri-articular injection of 1 millilitre of 2 per cent lignocaine, using a very fine needle. The joint is most easily entered from behind when the mouth is open and the condyle drawn forward. The point of entry is determined by palpation and is about half an inch anterior to the tragus of the ear.

Loose, recurrently subluxating joints can be injected in the same way with a mild sclerosant, such as 2 per cent phenol in glycerin and glucose or with 5 per cent ethanolamine oleate in order to induce a fibrous contraction of the capsule.

The only disturbing feature of these injections is an occasional temporary facial palsy brought on by the lignocaine; it is as well to warn the patient of the possibility beforehand.

Operative Surgery

Operation is only recommended after all conservative measures have failed and where there is an obvious meniscal displacement or obstruction with continued pain; particularly is this so if the lateral pterygoid has torn away from the front of the disc and the latter has drifted towards the back of the joint preventing closure of the teeth on that side. Meniscectomy will usually give immediate relief but this does not absolve the surgeon from having the occlusion checked and treated as well. Post-operative orthodontic supervision must also be available.

Acute cases

If orthodontic treatment in the acute case has failed after three months, and snapping or irregular movement is a persistent disability, then the removal of the articular disc is indicated.

Chronic cases with recurrent locking

Recurrent locking is a specific indication for operative intervention, but only when orthodontic treatment has been undertaken and has failed. It is sometimes necessary to open the bite as much as 5 or more millimetres. If the deformity or inconvenience from wearing an appliance is intolerable surgical intervention is then the only solution. Lesions of both temporomandibular joints are not uncommon, and sometimes locking or clicking develops on the second side after operation on the first. Surgery should not be undertaken on the second side until at least three months have elapsed from the first operation.

Surgical excision of the disc

The loose, thick or split disc is a mechanical block to smooth co-ordinated synchronous jaw movement. Its removal is a *sine qua non* for restoration of normal function. There is, however, the additional factor that in some cases one or both joints have developed hypermobility. By scarring the capsule as with operations on other joints, arthrotomy may help to limit this excessive movement. Arthritis is a probable occurrence in any damaged joint and the presence of a loose body

which is no longer a protection to the joint surface is likely to aggravate inflammatory change. Removal of the disc will not precipitate arthritic change, but before the significance of the underlying malocclusion in these cases was fully realized, surgery was undertaken without pre-operative or post-operative bite correction: from this fact has arisen the belief that operation may lead to arthritis.

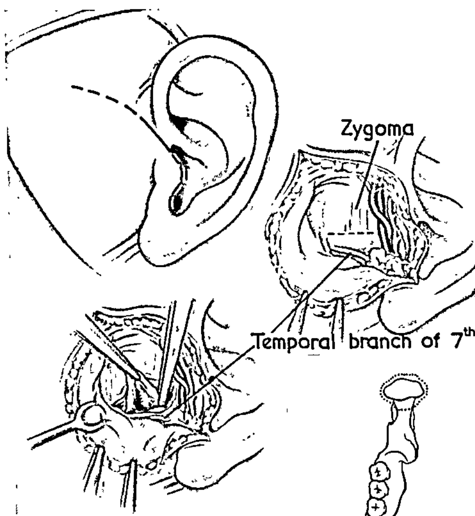


FIG. 77.—*Drawing of operation for temporomandibular meniscectomy. A vertical pre-tragal incision may be used, if the hair line is low. (By courtesy of the Editor, British Dental Journal.)*

Operative technique

General anaesthesia must be administered through a nasal tube because it must be possible for the surgeon to manipulate and close the jaw during operation. A vertical pre-auricular incision 3·5 centimetres in length extends upwards from approximately 1 centimetre in front of the base of the tragus at its lowest point.

The incision should be marked with dye, and the line of the articular eminence and zygoma should be identified by palpation and marked on the skin. The area is then infiltrated with approximately 4 millilitres of 1 in 100,000 adrenaline solution. The ear should be plugged loosely with wool soaked in antiseptic and the towels applied with Mastisol in such a way that the tragus and ear are covered. The branch of the facial nerve which supplies the frontalis muscle is easily damaged by retraction: this must therefore be gentle. Dissection must be slow and careful and haemostasis secured with fine-point diathermy forceps. Care must be taken to avoid the superficial temporal vein and artery, and as the incision is deepened on to the capsule of the joint it may be necessary to tie branches of these vessels. The secret of exposure depends upon the use of the blunt flat blade of a Kilner retractor, and miniature curved Mayo blunt pointed ophthalmic scissors. The joint is entered on its postero-lateral aspect by nibbling with the scissors (Fig. 77). The appearance of a bubble or two indicates that the joint is open. The scissors are then used to stretch the opening in the capsule in a vertical direction. One can then see the disc and it should be gripped with a pair of Dunhill forceps. Again using the curved scissors, the posterior and anterior remaining attachments are severed and as the disc is pulled towards the surface the curved blades are carried round the medial extremity of the disc which may well be 2 centimetres deep. At this point there may be profuse haemorrhage requiring the use of a suction nozzle. Immediately the disc is removed (Fig. 78) the mandible is elevated by the assistant to compress the condyle into the articular fossa. This invariably controls the haemorrhage. One small suture of 000 chromic catgut is used to repair the capsule: 000 plain interrupted stitches are used for subcutaneous fat and a running subcuticular nylon stitch closes the skin incision. This is tied over gauze. Vertical strips of 1-inch elastic strapping complete the dressing. A barrel bandage is applied.



FIG. 78.—An excised meniscus, showing erosion of its centre: it was 2·4 centimetres long.

The patient should be maintained on a fluid diet for three days and allowed only soft solids for the rest of the first week. The bandage may then be discarded and mobilization encouraged. No dental appliance is worn during the first week. If malocclusion is present the appliance should be worn again afterwards.

Alternative procedures

In cases of gross malocclusion unrelieved by conservative treatment, condylectomy is occasionally necessary. Division of the neck of the mandible has been practised in some clinics without arthrotomy and removal of the disc. The idea of this more extensive procedure is that the head of the mandible can then assume, in relation to the body, a position which suits the particular malocclusion.

Though the authors prefer the simple vertical pre-auricular incision, others use a more curved pre-auricular approach, splitting the tragus and turning down a flap containing the upper pole of the parotid gland (*see* Fig. 77).

The surgical approach to the joint for more extensive procedures than excision of the disc is probably easiest through a post-auricular incision at the base of the pinna, turning this forward with the incision across the cartilaginous meatus.

RESULTS OF TREATMENT

The following Table shows the treatments employed for temporomandibular joint disorder.

TABLE

	Percentage
Voluntary muscle control and exercises	17
Physiotherapy	31
Immobilization	7
Selective cuspal grinding	17
Joint injections—8 hydrocortisone; 2 sclerosant solutions	10
Training flanges	2
Orthodontic	6
Extractions—8 for wisdom teeth	20
Meniscectomy	5
Prosthetic appliances	79

Two or more lines of treatment were often used on the same patient, but the figures in the Table (Hankey, 1958) show the frequency of employment of each kind of treatment. Seventy-nine per cent were supplied with some form of removable prosthetic appliance because it was impossible by any other means to take the strain off the joint, relieve muscle spasm and provide a reasonable, balanced occlusion in centric relation.

Among the 21 per cent who were not provided with prosthetic appliances were those with bad habits or with only minor degrees of malocclusion which could be cured by selective grinding, muscle exercises or self-control.

Only 5 per cent required surgery of the joint and in all of them meniscectomy cured the pain.

The total percentage of cures was 60; 34 per cent were much improved but not entirely free from symptoms; 6 per cent failed to respond to treatment.

REFERENCES

Bauer, W. (1940). "Osteo-arthritis Deformans of the Temporomandibular Joint." *Amer. J. Path.*, **17**, 129.

Bennett, G. A. (1948). *The Joints in Pathology*. St. Louis; Mosby.

Blackwood, H. J. J. (1959). "The Developmental Anatomy and Pathology of the Intra-articular Disc." Unpublished paper read to Section of Odontology, Royal Society of Medicine, November 23, 1959.
Burman, M., and Sinberg, S. E. (1946). *J. Bone Jt Surg.*, **28**, 351.
Campbell, J. (1958). "Distribution and Treatment of Pain in Temporomandibular Arthrosis." *Brit. Dent. J.*, **105**, 393.
Cohen, Lord (1959). "Facial Neuralgias." *Brit. Dent. J.*, **107**, 9.
Costen, J. B. (1934). "A Syndrome of Ear and Sinus Symptoms Dependant Upon Disturbed Function of the Temporomandibular Joint." *Ann. Otol. etc., St. Louis*, **43**, 1.
— (1956). "Classification and Treatment of Temporomandibular Joint Problem." *Ibid.*, **65**, 35.
Craddock, F. W. (1951). *Prosthetic Dentistry*. 2nd ed. London; Kimpton.
— (1953). "Radiography of the Temporomandibular Joint." *J. dent. Res.*, **32**, 302.
Hankey, G. T. (1954). "Temporomandibular Arthrosis." Charles Tomes Lecture, Royal College of Surgeons of England, 1953. *Brit. Dent. J.*, **97**, 249.
— (1956). "Affections of the Temporomandibular Joint." *Proc. R. Soc. Med.*, **49**, 983.
— (1958). "Some Observations on Costen's Mandibular Syndrome." *Ibid.*, **51**, 225.
Harris, W. (1937). *The Facial Neuralgias*. London; Oxford University Press:
Last, R. J. (1954). "The Muscles of the Mandible." *Proc. R. Soc. Med.*, **47**, 571.
Lindblom, G. (1953). "Disorders of the Temporomandibular Joint." *Acta odont. scand.*, **11**, 1.
Moyers, R. E. (1950). "Electromyographic Analysis of Muscles in Temporomandibular Movement." *Amer. J. Orthodont.*, **36**, 481.
Rees, L. A. (1954). "The Structure and Function of the Mandibular Joint." *Brit. Dent. J.*, **96**, 125.
Robinson, M. (1946). "The Temporomandibular Joint: Theory of Reflex Controlled Nonlever Action of the Mandible." *J. Amer. dent. Ass.*, **33**, 1260.
Sarnat, B. G. (1951). *The Temporomandibular Joint*. Illinois; Thomas.
Shapiro, M. M. (1947). *Applied Anatomy of Head and Neck*. Philadelphia; Lippincott.
Sicher, H. (1947). "The Growth of the Mandible." *Amer. J. Orthodont.*, **34**, 30.
— (1951). "Functional Anatomy of the Temporomandibular Joint." In *The Temporomandibular Joint*. Ed. by Sarnat, B. G. Illinois; Thomas.
— (1952). *Oral Anatomy*. London; Kimpton.
Stones, H. H. (1956). "Facial Pain. Review of Aetiological Factors." *Proc. R. Soc. Med.*, **49**, 33.
Thompson, J. R. (1949). "The Rest Position of the Mandible and its Application to Analysis and Correction of Malocclusion." *Angle Orthodont.*, **19**, 162.
— (1951). "Temporomandibular Disorders, Diagnosis and Dental Treatment." In *The Temporomandibular Joint*. Ed. by Sarnat, B. G. Illinois; Thomas.
Tulley, W. J. (1957). "Muscles and the Teeth." *Proc. R. Soc. Med.*, **50**, 313.
Zimmerman, A. A. (1951). "An Evaluation of Costen's Syndrome." In *The Temporomandibular Joint*. Ed. by Sarnat, B. G. Illinois; Thomas.

SELECTED ABSTRACTS

Mandibular condyle

Development, growth and pathology

The development, growth and pathology of the mandibular condyle and its related structures were examined by BLACKWOOD (1959) in a series of 16 human foetuses and in 530 human temporomandibular joints removed from individuals in all age groups at routine necropsy examination. The arterial circulation of the heads of six new-born infants was perfused with radio-opaque and optically-opaque material, and the developing condylar regions of these specimens were examined microscopically.

A general account is given of the development and growth of the mandibular condyle and temporomandibular joint from early foetal life up to adult life. The development and histological structure of the vascular canals of the condylar cartilage is described in detail and the course and nature of the vascular system within these canals is demonstrated in the perfused specimens. The histological anatomy of the growing and adult temporomandibular joint is described and the average age for termination of endochondral bone growth in the mandibular condyle established. The mandibular condyle is also examined as a site of haemopoiesis in adult life. The pathological lesions encountered in the series of temporomandibular joints examined are described and these are classified and discussed under the following headings: (*a*) general diseases affecting the temporomandibular joint, (*b*) secondary tumours of the mandibular condyle, (*c*) mechanical injuries of the joint, (*d*) rheumatoid arthritis, (*e*) osteoarthritis, (*f*) lesions of the intra-articular disc, (*g*) age changes and (*h*) developmental anomalies of the joint. The study is illustrated by 198 photomicrographs and an account is also given of an investigation into the use of industrial nitrocelluloses as embedding media for animal tissues.

Pain in temporomandibular arthroses

Distribution and treatment

CAMPBELL (1958) reviewed the distribution and treatment of pain in temporomandibular arthroses. This is a baffling type of pain which cannot be explained by dentistry, neurology or injury. It is not relieved by intracranial section of the trigeminal nerve. Its occurrence in edentulous persons and those suffering occlusal breakdown suggests mandibular overclosure or displacement. This is not the sole cause, however, the condition having occurred in patients with immaculate occlusion. From 1,109 patients with temporomandibular disorder, 899 were selected for occlusal reconstruction; 20 types of facial pain were then listed. Pain occurred equally on both sides and the pain-distribution was remarkably symmetrical The common sites were the temporomandibular joint, gonial angle, ear, zygomatic arch, anterior part of the temple, and the submandibular space. Much pain also occurred in the suboccipital region, relieved coincidentally with the facial pain. Theoretically, these pains could be neuralgias of the nerves involved, but it is probably the muscles which are implicated. For example, dense concentrations of pain at the zygoma and gonial angle could be interpreted as pain at the origin and insertion of the masseter. Pain in the glands could be in the suprahyoid muscles. Pain in the joint itself results from the meniscus becoming the focal point of inordinate muscle tension or misdirected occlusal force. Occlusal reconstruction is effective for pain near the joints, occasionally for remote pain. Sudden violent pain with complete relief between the attacks suggests trigeminal neuralgia, while dull, deep pain is commonly associated with the temporomandibular syndrome. An unclassified group of cases demonstrated diverse pain-patterns; such pain should not be dismissed as psychoneurotic. Pain in the head and neck, even spreading to the shoulders and chest, may be due to muscle fatigue. That relief is obtained by removal of the focal pain is probably due to general muscular relaxation. Occlusal reconstruction is not simple. Its essence lies in estimating the *vertical dimension;* with the creation of a new dimension the mandible may shift horizontally. The general practitioner should, however, be able to ensure that the vertical dimension develops optimally in children, and does not collapse when a denture becomes necessary in later life. A practical case in a boy aged 10 years is described. In children, vague, unexplained earaches are common and may arise after removal of a key supporting tooth, suggesting impairment of the vertical dimension.

Discussion

In the DISCUSSION (1958) following Dr. Campbell's paper, Mr. Hankey emphasized that only those cases with pain had been considered. He agreed with the author's tabulation of common sites of pain and its muscular origin in many cases. Mr. Fairley said that his practice was confined to patients with natural dentition in whom the important

factor was the registration of the eccentric relation. Treatment was directed to stabilization of the mandible and maintenance of the vertical dimension. Patients with unilateral pain responded quickly to a diagnostic splint. Symptoms were relieved by freedom from dorsal displacement rather than increase in vertical dimension. He discounted radiography in diagnosis. Mr. Heylings said that prevention was in the hands of the general practitioner. In occlusal restoration the maintenance of all movement in both joints was more important than height and depth. He asked why the author had not correlated pain with the anatomical distribution of the sensory nerves. Professor Hitchin agreed that pain of muscular origin was probably the most important factor. He asked for a definition of immaculate occlusion. Mr. Mumford attached significance to the time-factor of pain and its character. Was it momentary or did it come in a flash and then persist as a dull pain? Mr. McIvor believed muscle imbalance to be particularly important in the temporomandibular joint. Mr. Anderson asked whether Dr. Campbell found a low degree of masticatory function in patients experiencing facial pain. He also suggested that too great a vertical height in dentures might be as important a cause of pain as overclosure. Dr. Lammie suggested that "taking the bite" required an almost hypnotic technique on the part of the dental surgeon. Mr. Cubie asked whether Dr. Campbell had met cases of deafness due to infringement by the mandible of the posterior part of the condyle on the thin tympanic plate. Dr. Campbell replied fully and individually to his questioners. "The occlusal planes had to balance in all mandibular excursions in accord with the action of the temporomandibular joint. The vertical and horizontal dimensions of the jaws had to harmonize with the rest of the mechanism and the neuromuscular reflexes had to be in synergistic harmony . . . The temporomandibular joint was difficult to radiograph and the films and the clinical record often contradicted one another; none the less, although he was using radiography less and less, he had no intention of abandoning it . . . We had to bring fresh thinking to the so-called facial neuralgias: the medical profession had shouldered the heavy responsibility of neuralgia too long; we [dental surgeons] have learned that we can help a proportion of their cases."

Costen's syndrome

WING (1959) discussed the status of Costen's syndrome. This is basically a disturbed function of the temporomandibular joint following loss of molar support, an associated increased overbite and decreased vertical dimension producing abnormal ear and head conditions. Costen's criteria are impaired hearing, a "stuffy" sensation and dull pain in the ears, tinnitus and a snapping noise when chewing, dizziness, sinus symptoms and a burning feeling in the throat, tongue and nose. Costen regarded these symptoms as constant and anatomically sound, but more recent workers disagree. Cheraskin and Langley in 1956 admitted that derangements in the oral cavity may lead to mechanical and neurological manifestations, but emphasized recognition of the relationship rather than specific terminology. Among the causes of pain, Costen included pressure on the nerve supply of the dura on closure, pressure on the auriculo-temporal nerve, pressure on the chorda tympani nerve. Other workers have described pressure effects on the auriculo-temporal nerve but Sicher's view in 1948 was that no anatomical basis exists. He regarded impingement of the condyle on the vascular and highly innervated tissue behind the meniscus as the main source of joint pain and of some referred pain, attributing extra-articular pain to muscle spasms. Déchaume and his colleagues in 1953 suggested that pain arises from irritation along the sympathetic fibres found periarterially in proximity to articulations and believed it to be accompanied by secondary signs. Costen claimed that ear symptoms resulted from bite anomalies allowing occlusion of the eustachian tube through condylar retrusion but his findings have not been substantiated. Their incidence is now thought to be less frequent and possibly coincidental. Head and ear noises are now attributed to the clicking or grating sounds within the joint from the presence of osteophytes, to a disturbance of the condyle-meniscus relationship or to an actual mechanical contact between the condylar head and the articular eminence.

Facial neuralgias

COHEN (1959) discussed facial neuralgias. The perception of pain depends firstly u the integrity of the neural mechanisms for reception and conduction of a painful stimi and secondly upon the "sensorium" or "psyche". Wherever a sensory nerve is sti lated, the resulting pain is referred to the peripheral distribution of the same or a rel nerve, in the latter case properly termed "referred pain". Neuralgia indicates p corresponding to the known anatomical nerve distribution; when due to a gross pat logical lesion directly involving the nerve, it is symptomatic or secondary. The condi known as "tic" is primary. Primary neuralgia is associated with momentary paro mal pain with almost complete remission between spasms; paroxysms may also precipitated by superficial stimulation of "trigger zones". The cranial nerves implica are the trigeminal, glossopharyngeal, facial and superior laryngeal. The mechanism probably similar to that initiating epilepsy. Supporting evidence includes the paroxys nature of the pain, the presence of trigger zones, a refractory period and recurre Moreover, incomplete destruction of the ganglion is followed by regeneration and ret of pain, while pre-ganglionic root section is only effective if performed early. The tribution and communications of the fifth nerve make trigeminal neuralgia of g dental importance. Since no dental or buccal condition accurately simulates it, e diagnosis should be simple and dental treatment thus avoided. Of lesser dental sig cance are the other forms of cranial nerve neuralgia. Glossopharyngeal pain is ident in quality with that of tic douloureux and a paroxysm is often "triggered" by swall ing, chewing, yawning or coughing. In seventh nerve neuralgia the ear pain may mistaken for referred dental pain, while in great auricular neuralgia pain is often at the angle of the jaw. Lesions producing symptomatic or secondary neuralgia may intracranial, appertaining to the bony cranial base, and extracranial. The last includ retropharyngeal tumour and Frey's auriculo-temporal syndrome. Localized facial p is caused by disease of the teeth and jaws, sinuses and antra, ears, eyes, temporomandib joint and muscles of mastication. Among the rare referred pains felt in the jaws are th arising from coronary disease, neck lesions and lesions of the oesophagus and car end of the stomach. Two syndromes of vascular pain which may involve the face migrainous neuralgia and giant-celled arteritis. An important form of facial neural is the "atypical", of psychogenic origin, generally occurring in menopausal women only aggravated by surgery. There is positive evidence of psychiatric disturbance often of drug addiction.

Dental diagnosis of pain

Temporomandibular joint and myofascial trigger areas

FREESE (1959) discussed the temporomandibular joint and myofascial trigger area the dental diagnosis of pain. A trigger area is a small, circumscribed hypersensitive a which on stimulation sends impulses to the central nervous system, giving rise to refer pain. One trigger area may produce another in its reference zone, the mechanism be repetitive. Causes of trigger areas include sudden trauma to musculoskeletal structu excessive exercise, chill, immobilization, an acute visceral lesion, acute arterial occlus in the extremeties, rupture of an intervertebral disc with nerve root pressure, emotio stress. Many predisposing factors also exist. The mechanism of the pain is proba pathophysiological, producing a self-perpetuating cycle. In general, the site of the p assists diagnosis. Pain in the teeth is pathological, rarely psychogenic. Mouth throat pain is local or referred from trigger areas in the pterygoid or digastric and ge hyoid muscles. Pain in the face and head is more complex. After elimination of causa factors, the myofascial trigger areas are located. If the reference zone itself beco a trigger area, differential diagnosis is difficult. Muscle spasms also cause head and n pain. Of special dental interest is the mandibular muscle spasm syndrome, compris mandibular dysfunction and emotional disturbance. Temporomandibular joint disor may be traumatic, neoplastic, infectious or arthritic. The last and commonest is due rheumatoid arthritis or osteoarthritis, clinically and radiographically difficult to differe ate until degenerative joint changes occur. Severe pain may produce spasms of

muscles supplied by the same spinal cord segments as the joint. Temporomandibular pain can also be referred, palpation of a trigger area in the masseter muscle causing pain in the joint. Furthermore, a deep hyperalgesia in the reference zone may initiate pain on palpation of the joint. Diagnosis is confirmed by eliminating the trigger area. Another common zone of reference for pain is the ear.

Occlusal rehabilitation

POSSELT (1959) gives an account of a number of functional abnormalities of the masticatory system in adults and points out that complications due to dental extractions or defective fillings include overclosure and occlusal interference during closure or gliding movements. Functional disturbances may result in pathological changes such as muscle spasm, periodontal trauma and arthrosis of the temporomandibular joint. Muscle spasm may be eliminated by employing occlusal adjustment, relaxation and physical therapy. Prosthetic occlusal reconstruction is of particular value in the management of facial pain and derangement of the temporomandibular joint. Before treatment is planned it is important to establish centric relation. Normal muscle tone should be restored in cases of posterior displacement of the condyles. An overlaid splint is employed as a temporary measure, but a similar effect may be achieved by means of an upper bite (Hawley) plate with a groove for the lower incisors. Radiographs of the temporomandibular joint are of assistance in defining the position of the condyles. Complicated reconstruction work should be avoided in patients suffering from anxiety and stress, especially when the dental problem is relatively unimportant. From this point of view, a temporary splint is to be preferred. In order to obviate the risk of caries, however, the patient should be warned to take great care in carrying out the instructions about the method of applying the splint.

REFERENCES

Blackwood, H. J. J. (1959). *The Development, Growth and Pathology of the Mandibular Condyle*. M.D. Thesis. The Queen's University of Belfast.
Campbell, J. (1958). *Brit. dent. J.*, **105**, 393.
Cohen, Lord (1959). *Brit. dent. J.*, **107**, 9.
Discussion (1958). *Brit. dent. J.*, **105**, 402.
Freese, A. S. (1959). *J. Amer. dent. Ass.*, **59**, 448.
Posselt, U. (1959). *Dent. Pract.*, **9**, 255.
Wing, G. (1959). *Aust. dent. J.*, **4**, 98.

ISLET-CELL LESIONS OF THE PANCREAS

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The interest of physician, surgeon and pathologist in islet-cell lesions of the pancreas has increased in recent decades. Patients exhibiting these lesions may present with obscure symptoms which must be evaluated with care. Early detection and definitive treatment is mandatory to prevent gross errors in management with serious sequelae. Three broad entities may be considered:

(1) Lesions of the islets of Langerhans associated with an increased production of insulin.

(2) Islet-cell lesions in which there is no known accompanying aberration of normal physiology.

(3) Lesions of the islet cells associated with and probably related to peptic ulceration of the upper gastro-intestinal tract.

HISTORICAL ASPECTS

More than 90 years ago Langerhans (1869) described the tiny islets in the pancreas which bear his name but this discovery remained only an interesting histological curiosity for many decades. An incidental necropsy finding by Nicholls (1902) was the earliest pathological report of an adenoma of the islet cells. Although Minkowski (1893) had demonstrated the presence of an internal secretion of the pancreas which affected the metabolism of sugar and Schafer (1895) postulated that this secretion was derived from the islets of Langerhans, confirmation of this relationship awaited the elaboration of insulin by Banting and Best in 1922. The subsequent detection of the hypoglycaemic state in diabetic patients treated with insulin stimulated Harris (1924) to suggest the concept of hyperinsulinism which might be brought about by the presence of a hyperfunctioning tumour of the islets of Langerhans. The experimental production of hyperinsulinism was achieved by Herxheimer (1926) who ligated the pancreatic duct in a chicken with resultant hyperplasia of the islet cells and death due to hypoglycaemia.

Surgical interest in islet-cell lesions was aroused by Mayo (1927) who operated upon a patient with hypoglycaemia and found an islet-cell carcinoma with hepatic

metastases. Biochemical techniques demonstrated that the cells of the carcinoma elaborated insulin in large amounts and established the clinical correlation of hyperinsulinism with islet-cell tumour. It was just 31 years ago, in March 1929, that the late Roscoe Graham of Toronto produced the first surgical cure of hyperinsulinism by the successful removal of an insulin-producing islet-cell adenoma. About 500 cases of hyperinsulinism produced by lesions of the islets of Langerhans have now been described.

In 1955 Robert Zollinger and Edwin Ellison emphasized an apparently significant relationship between islet-cell tumours and peptic ulcers of the upper alimentary tract. Since that time over 100 cases of co-existing islet-cell tumours and peptic ulcers have been described.

PATHOLOGICAL FEATURES

Benign lesions

Adenoma

A benign solitary adenoma occurs typically as a firm discrete nodule, varying from a few millimetres to several centimetres in diameter (*see* Fig. 80). This tumour is most frequently located in the body or tail of the pancreas, which is not surprising since the greatest concentration of normal islets occurs in this region. Occasional ectopic islet-cell adenomas have been reported in aberrant pancreatic tissue found in the gastrosplenic omentum, hilum of the spleen, posterior to the pancreas and in the wall of the duodenum. The solitary adenoma presents a reddish or lilac colour contrasting with the adjacent yellow pancreatic tissue. A capsule commonly envelops the adenoma.

Warren (1926) emphasized the histological criteria for establishing the diagnosis of a benign islet-cell adenoma (*see* Fig. 82): (1) cellular morphology and arrangement resembling normal islets, (2) a mass at least one millimeter in diameter and (3) the presence of a definite capsule.

Multiple adenomas.—In 12 per cent of patients multiple adenomas occur and up to ten discrete tumours scattered throughout the pancreas have been described. The detection of microscopic adenomas depends upon careful histological study of resected pancreatic tissue.

Adenomatosis.—In rare instances adenomatosis of the islet cells is encountered with the histological finding of innumerable islet-cell adenomas diffusely scattered throughout the pancreas.

Hyperplasia of the islet cells

Hyperplasia or hypertrophy of the islet cells is rare and a controversial cause of hyperinsulinism. Campbell (1958) stated that hyperplasia exists in both an infantile and adult form. The pancreas is grossly normal. Histologically there is an increase in both number and size of the islets throughout the pancreas (*see* Fig. 85). Differentiation from microscopic adenomas is based on the lack of encapsulation of the hyperplastic islets which may be several times the normal size.

Borderline malignancy

Borderline malignancy refers to a questionable group of solitary islet-cell adenomas in which certain histological features are suggestive of malignancy. The gross appearance is indistinguishable from that of a benign solitary adenoma. Histologically there may be lack of encapsulation, local invasion and cytological features of grade 1 malignancy. In spite of the microscopic findings, metastases have not been reported.

Carcinoma

Carcinoma of the islet cells is an uncommon lesion. It appears as a large, hard, diffusely infiltrating tumour in the pancreas which spreads rapidly to the regional nodes and to the liver. Late metastases occur in multiple sites throughout the body. Histological sections of islet-cell carcinoma frequently reveal a high grade of malignancy.

Non-functioning tumours

Many islet-cell lesions (50–80 per cent) are not associated with an increased production of insulin. Non-functioning tumours are most frequently discovered at operation or necropsy. The reported incidence of islet-cell adenomas found at routine necropsy is about one in one thousand. This incidence increases when greater attention is directed to the pancreas, and in a careful study of 500 pancreatic specimens (Pease, 1947) six microscopic and two pea-sized adenomas were detected.

Zollinger-Ellison syndrome

The association of islet-cell tumour and peptic ulcer of the upper gastro-intestinal tract has been termed the Zollinger-Ellison syndrome. Although the pathology of this syndrome is still uncertain, several features have become apparent. The peptic ulcer is often in an unusual location, such as the oesophagus, second and third portions of the duodenum and upper jejunum. The tendency to produce ulceration is marked, illustrated by the frequency of multiple ulceration and persistent recurrence despite repeated surgical measures.

In the Zollinger-Ellison syndrome the islet-cell lesions demonstrate several unusual characteristics when they are compared to islet-cell tumours which are not associated with peptic ulceration.

(1) The incidence of malignancy is higher in the Zollinger-Ellison group than in other islet-cells lesions, but the grade of malignancy is low (*see* Fig. 86) and the tumour usually exhibits very slow growth.

(2) Histological study of islet-cell tumours for cytoplasmic granulation is a difficult procedure. In the Zollinger-Ellison syndrome no specific granulation can be detected in most instances, and Ellison (1959) now refers to these lesions as islet delta-cell "ulcerogenic" tumours of the pancreas. *Beta* granules which are associated with insulin production have been described in a few patients.

(3) In many patients with this syndrome adenomas are also noted in other endocrine glands, including the parathyroids, anterior pituitary and adrenal cortex.

CLINICAL FEATURES OF HYPERINSULINISM

Hyperinsulinism is a condition in which excess quantities of insulin are produced by a functioning lesion of the islets of Langerhans. The clinical features of this entity are numerous and varied. Mild reactions include hunger, weakness, faintness, perspiration and palpitation. These symptoms may be due to an adrenaline response associated with a rapid fall in blood sugar levels. Severe reactions are related to cerebral hypoglycaemia and may mimic the entire range of neurological and psychiatric disorders. Common manifestations include headache, confusion, disorientation, abnormal behaviour, transient paresis, stupor, coma, and convulsions.

Benign lesions

Adenoma

A benign solitary adenoma is the most frequent cause of hyperinsulinism. No relationship exists between the size of the adenoma and the severity of the condition it evokes. The smallest functioning islet-cell adenoma recorded, which measured only 2·5 millimetres in diameter (Lopez-Kruger and Dockerty, 1947), produced severe hypoglycaemia.

Multiple adenomas.—More than one islet-cell adenoma may be present in a patient with hyperinsulinism. The unsuspected presence of multiple adenomas may be responsible for early recurrence of the condition following removal of an apparent solitary lesion.

Adenomatosis.—Two cases of adenomatosis of the islet cells with hyperinsulinism have been reported in Great Britain (Bickerstaff and his colleagues, 1955; Garland, 1957). Functional adenomatosis of other endocrine glands, particularly of the parathyroid and pituitary may be an associated finding. A definite hereditary tendency has been found in some of these patients (Wermer, 1954).

Hyperplasia of the islet cells

Hyperplasia of the islet cells associated with hyperinsulinism has been reported in infants born of diabetic mothers (Campbell, 1958). An elevated maternal blood sugar stimulates an overgrowth of the foetal islets of Langerhans. Following birth, hypoglycaemic coma and death of the child rapidly occur unless prompt and effective glucose therapy is instituted. In the adult islet-cell hyperplasia is a rare cause of hyperinsulinism.

An increase in the number and size of the islets of Langerhans may occasionally be discovered at necropsy in infants dying of unrelated disease, in whom there has been no evidence of hyperinsulinism nor of maternal diabetes (Davey, 1959). The significance of this finding is not clear. Unexplained hyperplasia or hypertrophy of the islets may also occur in association with multiple adenomas and adenomatosis.

Borderline malignancy

Borderline malignant lesions are probably benign (Duff and Murray, 1942), since in no instance has the post-operative clinical course confirmed the presence

of malignant disease. Shaw (1956) proposed that this suspicious group of islet-cell adenomas is a stage towards those that are frankly malignant and it may be that excision of the lesion has effected a cure of an early carcinoma.

Diagnosis

History

The diagnosis of hyperinsulinism pre-operatively must be made with caution. A history of recurrent attacks suggesting hyperinsulinism should be corroborated by relatives or friends whose descriptions are often more accurate and valuable than those of the patient. Attacks due to true hyperinsulinism as differentiated from functional hypoglycaemias are usually progressively severe, occur when fasting or during exertion and eventually cannot be controlled by dietary regulation.

Examination and special investigations

Examination of the patient must be complete to eliminate the extra-pancreatic causes of hypoglycaemia. A fasting blood sugar below 50 milligrams per cent on repeated occasions has been considered essential for a diagnosis of hyperinsulinism. This may be induced by a provocative low carbohydrate diet, by fasting and exercise or by a prolonged starvation test up to 72 hours. The fasting test may be combined with exercise in an effort to precipitate an attack. We believe that the most essential characteristic of hyperinsulinism is intolerance to fasting. The glucose tolerance curve is not diagnostic of hyperinsulinism, but may be suggestive with a late, low sugar level. It is also of value in excluding other causes of hypoglycaemia. Electroencephalographic patterns of dysrhythmia which revert to normal with rising blood sugar levels may be an aid in identifying neurological symptoms of hyperinsulinism and thereby assist in excluding other organic cerebral disease.

Diagnostic criteria

Whipple's triad (1944) emphasizes the surgical prerequisites for the diagnosis of hyperinsulinism.

(1) The attacks come on characteristically in the early morning during the fasting period before breakfast or after severe mental or physical effort when the sugar reserves are low.

(2) During the attacks or spells or after a fast of from 12 to 24 hours the blood sugar levels are always below 50 milligrams per cent.

(3) The victims are brought back to a normal state, that is, recover from whatever their pattern may be, on the administration of sugar by mouth or vein.

In addition, Allan (1958) proposed three more essential criteria.

(4) Symptoms must be severe enough to cause stupor or loss of consciousness.

(5) Symptoms must recur despite adequate dietary regulation.

(6) Extra-pancreatic causes of hypoglycaemia must be excluded.

If these dicta are followed, the diagnosis of hyperinsulinism will be made with ease in most instances and few patients will be subjected to fruitless pancreatic exploration. If the investigation is inconclusive, as it may be in the early stages

of a functioning islet-cell lesion, the patient should be re-assessed at a later date when adequate data may be available to establish the correct diagnosis.

DIFFERENTIAL DIAGNOSIS OF HYPERINSULINISM

The differentiation of hyperinsulinism from other causes of hypoglycaemia may be difficult. Hypoglycaemia is a symptom-complex characterized by a low blood sugar producing decreased cerebral metabolism. The aetiology of hypoglycaemia may be considered briefly as follows.

(1) *Insulin overdosage* is the commonest cause, typically observed in the poorly controlled diabetic with an insulin reaction. Self-administration of insulin in a non-diabetic due to psychogenic or other factors must not be overlooked.

(2) *Extra-pancreatic hypoglycaemia* is a broad group containing a multiplicity of both common and bizarre diseases. Hepatic, adrenal and pituitary lesions including hepatitis, cirrhosis and neoplasia may be associated with hypoglycaemia. Recently non-pancreatic mesodermal tumours have been described which produce hypoglycaemia (Miller, Bolinger and Friesen, 1959). Functional hypoglycaemia is a common but ill-defined category in which a functional disorder is present, usually unrelated to a recognizable anatomical lesion. Renal glycosuria, nervous inbalance and dietary disorders are included in this group.

(3) *Organic hyperinsulinism* causing hypoglycaemia is due only to lesions of the islets of Langerhans.

(4) *Idiopathic hypoglycaemia* is a generalization encompassing those patients in whom no cause or satisfactory explanation for the hypoglycaemia can be determined.

CLINICAL FEATURES OF THE ZOLLINGER-ELLISON SYNDROME

The presenting clinical features in patients with the Zollinger-Ellison syndrome are those of a peptic ulcer or one of its complications. Early stomal ulceration following an acceptable surgical procedure for peptic ulcer, multiple ulceration, ulcers in unusual sites or a palpable pancreatic tumour in a patient with peptic ulcer are all features which should direct the surgeon's attention to this entity. Gastric hypersecretion and hyperacidity particularly at night, is a characteristic finding in almost all patients. Diarrhoea has been a prominent symptom in several instances and may be due to the elevated volume of gastric secretion. With some exceptions, hyperinsulinism is rarely found in this syndrome. If other endocrine gland adenomas are present they are non-functioning in most instances.

TREATMENT

Surgical therapy is mandatory for lesions of the islets of Langerhans causing hyperinsulinism. Indecision may result in repeated hypoglycaemic attacks with permanent cerebral damage or even fatality.

We administer an intravenous glucose infusion immediately before and during the operation in order to maintain a satisfactory blood sugar level. Pre-operative steroid therapy has also been advocated, not only to elevate the blood sugar, but

also in an attempt to prevent the mysterious hyperthermia which has been responsible for several deaths in the post-operative period (Conn and Seltzer, 1955).

Simple enucleation of a solitary adenoma has been the procedure of choice in the past. Recently subtotal pancreatectomy has been advocated for all adenomas in the pancreatic body and tail to lessen the possibility of overlooking residual non-palpable adenomas (Warren and Cattell, 1959).

Case histories

Case 1

Mrs. N. Y., a 63-year-old housewife, was admitted to hospital on January 9, 1958, complaining of crampy, intermittent upper abdominal pain associated with weakness and sweating of 18 months' duration. A more significant history was obtained from the family, who had noticed that the patient was confused and behaved peculiarly during these attacks.

General examination was within normal limits. Fasting blood sugars on several occasions ranged from 28 to 69 milligrams per cent. A glucose tolerance curve dropped to 35 milligrams per cent at 5½ hours. A "long fast" was instituted, and 17 hours after food had been withheld the patient complained of abdominal pain, and became irrational and confused. Her blood sugar was 27 milligrams per cent, and she responded rapidly to intravenous glucose administration. On another occasion, while fasting, an electroencephalogram revealed generalized cerebral dysrhythmias. The blood sugar was 69 milligrams per cent. Five minutes after glucose was given, the electroencephalogram improved to essentially normal limits.

At operation a discrete nodule about 1·5 centimetres in diameter was palpated within the body of the pancreas on its postero-superior aspect (Fig. 79). A distal pancreatic resection was performed including removal of the spleen.

Several hours post-operatively the blood sugar had risen to 470 milligrams per cent. Insulin was administered for several days, and the fasting blood sugar gradually receded to normal levels during the second post-operative week. Convalescence was prolonged by a pancreatic fistula, which closed spontaneously. This patient has remained clinically well with no further hypoglycaemic attacks.

Histological sections revealed a well-demarcated tumour nodule lying within the pancreatic tissue. A noteworthy feature was the lack of a true capsule. The nodule was composed of cords and masses of uniform cells resembling those of the islets of Langerhans. Mitotic figures were rare, and on the basis of cellular morphology, despite the lack of encapsulation, this tumour was considered to be a benign islet-cell adenoma. The remainder of the pancreatic tissue was normal.

At operation adequate exposure for seeing the entire pancreas is required. The head, body and tail must be carefully inspected and palpated. Exploration is facilitated by mobilization of the duodenum, and the body and tail may be freed by incising the peritoneum inferiorly. Enucleation of an adenoma is recommended for those tumours found in the head of the pancreas. The following case report illustrates the ideal indication for this procedure.

Case 2

Mrs. M. O., an obese 38-year-old housewife, was admitted to hospital on June 10, 1959, with a history of attacks of weakness and confusion of four months' duration. Personality changes, including hostility and belligerence accompanying these attacks had concerned her family and physician and she volunteered to enter a mental hospital for observation. Psychiatric illness was excluded, but during this period, after several hours without food, she became comatose on two occasions responding each time to intravenous glucose administration. The patient noticed that her symptoms resembled closely those of other patients following insulin shock therapy.



FIG. 79.—Gross specimen of distal pancreas from Case 1. Arrow indicates islet-cell adenoma which has been incised.



FIG. 80.—Gross specimen of benign islet-cell adenoma excised from the head of the pancreas (Case 2).

Physical examination on admission was essentially normal. Fasting blood sugar levels ranged from 39 to 47 milligrams per cent. A glucose tolerance curve dropped to 45 milligrams per cent at 4½ hours. A "long fast" was instituted, and 36 hours after food had been withheld the patient became stuporous. The blood sugar level was 39 milligrams per cent, and she recovered rapidly with intravenous glucose injection.

At operation a firm mass was palpable within the head and neck of the pancreas overlying the superior mesenteric vessels. The pancreas was incised anteriorly, and a circumscribed tumour nodule two centimetres in diameter was "shelled out" of the pancreatic tissue (Fig. 80).

A blood sugar level taken immediately after the removal of the nodule was 298 milligrams per cent, and remained above 200 milligrams per cent throughout the day. Fasting blood sugar levels gradually dropped to normal values by the tenth post-operative day. The convalescent period was uneventful except for a pancreatic fistula which closed spontaneously. The patient has remained symptom-free since her operation.

Histological sections of the tumour nodule demonstrated well-differentiated cells resembling those of the islets of Langerhans. Despite the absence of a well-defined capsule, the pathological diagnosis was a benign islet-cell adenoma.

Post-operatively, a transient hyperglycaemia, although an inconsistant finding, is a welcome sign, and usually indicates removal of the offending lesion (Somogyi, 1959). The blood sugar may be sufficiently elevated to require insulin administration for several days. A temporary pancreatic fistula occasionally develops, but usually heals spontaneously. Diabetes mellitus rarely occurs following subtotal pancreatic resection.

If the surgeon elects the lesser procedure of enucleation for an adenoma in the body or tail, he must accept the possibility of the presence of concomitant non-palpable adenomas. If more than one adenoma is discovered in the body or tail of the pancreas, left hemi-pancreatectomy is the procedure of choice.

Case 3

Mrs. J. T., a 33-year-old housewife, was admitted to hospital in November 1949. She complained of attacks of disorientation and confusion of 14 months' duration. On one occasion the patient was returning home by bus and regained her senses in a police station. She had apparently left the bus at the wrong town, wandered into a strange house and had been arrested as a suspicious character. She continued to have attacks while following a dietary regimen for functional hypoglycaemia and, on another occasion, had a transient left-sided hemiplegia.

Physical examination was essentially normal and her fasting blood sugar was 40 milligrams per cent. A glucose tolerance test showed a drop to 60 milligrams per cent at six hours.

On November 29, 1949, the abdomen was explored. A solitary adenoma two centimetres in diameter was discovered within the tail of the pancreas and was excised (Fig. 81). Post-operative blood sugars remained within normal limits and her convalescence was uneventful.

Histological sections demonstrated an encapsulated tumour whose histological features were typical of a benign islet-cell adenoma of the pancreas (Fig. 82).

This patient remained symptom free for almost 9 years, until 1958. On this occasion, aged 42 years, she presented with a three months' history of recurrent attacks of weakness and dizziness. On one occasion she had been comatose for 2½ hours.

Her physical examination was essentially negative. Fasting blood sugar level varied from 46 to 70 milligrams per cent. A "long fast" was performed, and the patient became confused and disorientated 22 hours after food had been withheld. The blood sugar was 56 milligrams per cent, and immediate recovery followed glucose injection.

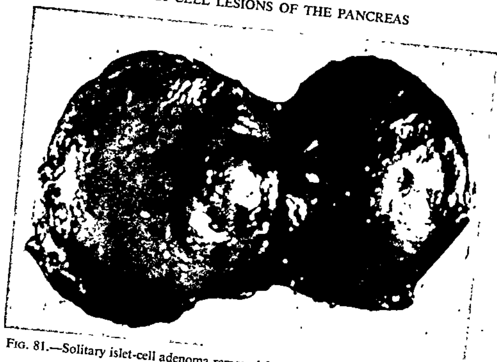


FIG. 81.—Solitary islet-cell adenoma removed from the tail of the pancreas in 1949 (Case 3).

FIG. 82.—Photomicrograph of solitary benign islet-cell adenoma from Fig. 81 (×600).

With a presumptive diagnosis of recurrent hyperinsulinism, this patient was operated upon again on July 31, 1958. The pancreas was carefully palpated, and two discrete, rubbery nodules about one centimetre in diameter were found within the pancreatic tail (Fig. 83). Partial pancreatectomy and splenectomy were carried out, removing the body and tail of the pancreas.

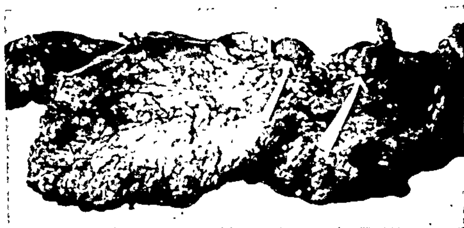


FIG. 83.—Gross specimen of distal pancreas from Case 3 following second operation (1958). Specimen has been incised and arrows indicate two palpable adenomas in the tail.

On the first post-operative day the blood sugar rose to 374 milligrams per cent and gradually dropped on succeeding days to normal levels. Her convalescence was uneventful, and she has remained clinically well and free from attack since operation.

Serial sections of the body and tail of the pancreas revealed the presence of 10 small islet-cell adenomas ranging from 0·3 to 1·0 centimetre in diameter (Fig. 84). Six of these were in the tail of the pancreas. The cellular structure of these encapsulated lesions resembled that of the islets of Langerhans, and the pathological diagnosis was multiple, benign islet-cell adenomas (recurrent).

In spite of the fact that this patient remains clinically well, we cannot rule out the

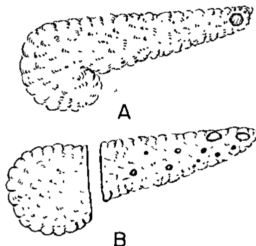


FIG. 84.—Case 3: *A*—Diagrammatic representation of pancreas illustrating site of initial islet-cell adenoma removed from pancreatic tail in 1949. *B*—Diagram indicates sites of ten multiple adenomas discovered in resected pancreatic tissue (1958).

possibility of adenomas in the residual pancreas, particularly in view of the fact that only two of the ten known lesions were palpable by the surgeon at operation.

If no palpable tumour is found within the pancreas, a search should be made for an ectopic islet-cell adenoma in the regions where aberrent pancreatic tissue is likely to occur.

In a situation where painstaking exploration has failed to reveal a tumour nodule, if organic hyperinsulinism has been diagnosed by careful pre-operative assessment, " blind" subtotal distal pancreatectomy is justified for several reasons:

(1) A functioning adenoma may be too small to be palpable.

(2) Microscopic multiple adenomas or islet-cell hyperplasia may be the aetiologic factor.

(3) Symptomatic relief has occurred in patients treated by partial pancreatectomy in whom the resected tissues were histologically normal.

Case 4

The following report was obtained from the files of the Department of Pathology of the University of Alberta.

Mr. J. F., a 39-year-old baker, was admitted to hospital complaining of increasingly severe attacks of weakness, dizziness and syncope of five years' duration. These attacks usually occurred when he was hungry.

Physical examination was normal. Fasting blood sugar levels ranged from 34 to 76 milligrams per cent, and a glucose tolerance test revealed a level of 23 milligrams per cent at four hours.

At operation elsewhere, subtotal pancreatectomy with splenectomy was performed, and the fasting blood sugar levels returned to normal following this procedure.

The post-operative course was stormy, complicated by wound dehiscence and

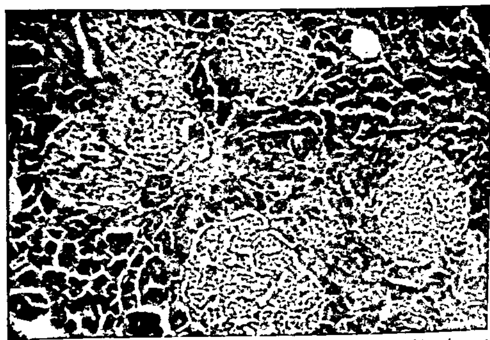


FIG. 85.—Photomicrograph from Case 4 illustrating islet-cell hyperplasia with an increase in number and size of the islets of Langerhans (×300).

peritonitis and the patient died during the second post-operative week. A necropsy could not be obtained.

Histological study of the surgical specimen disclosed an increase in the number and size of the islets of Langerhans throughout the pancreas (Fig. 85). Multiple serial sections of the resected tissue failed to reveal an adenoma, but some of the unencapsulated islets were unusually large, up to 300 microns in diameter, averaging 1½–2 times the normal size. The pathological diagnosis was hyperplasia and hypertrophy of the islets of Langerhans.

If subtotal pancreatectomy is performed, removal of the spleen is advocated for these reasons.

(1) Proximal ligation of the splenic artery reduces blood loss and facilitates the pancreatic resection.

(2) Danger of delayed splenic rupture or haemorrhage following trauma during operation is avoided.

(3) Possible sites of aberrant islet-cell tissue include the splenic hilus and the gastrosplenic omentum, and these areas are examined more carefully with splenectomy.

(4) Although a rare occurrence, trauma to the pancreas may produce localized thrombosis in the splenic vein, with resultant portal hypertension and oesophageal varices.

The complication of thrombophlebitis following splenectomy may be avoided or controlled with anticoagulant therapy.

Total pancreatectomy for hyperinsulinism has been employed on rare occasions with at least one favourable result in which a microscopic adenoma was found in the head of the pancreas (Priestley, Comfort and Radcliffe, 1944). Total resection should never be employed until a painstaking search has eliminated the possibility of an ectopic islet-cell adenoma.

The treatment of an islet-cell lesion in which there is no known accompanying aberration of normal physiology depends upon the circumstances in which this lesion is detected. The inadvertent discovery of a pancreatic tumour at abdominal exploration is an indication for excision of the tumour if this can be performed without undue risk to the patient. Diagnosis by means of frozen section may be a valuable guide for immediate management of the lesion.

Islet-cell tumours of the pancreas discovered in association with primary or recurrent ulceration of the upper gastro-intestinal tract should be excised whenever possible. This resection not only removes the neoplasm, but there is some evidence to indicate that it may favourably affect the ulcer tendency. Nevertheless, a patient with the Zollinger-Ellison syndrome requires a very radical gastrectomy combined with vagotomy in an effort to control the peculiarly intractable and frequently lethal ulcer diathesis in this condition.

Case 5

Mr. T. C., a 29-year-old male, was admitted to hospital with a history of epigastric pain of five months' duration. A barium meal examination demonstrated a duodenal ulcer, and he was discharged on a medical regimen.

He was re-admitted in April, 1950, with a persistent exacerbation of abdominal pain despite medical management. The pain was accompanied by nausea, vomiting, diarrhoea, and melena on one occasion. Examination revealed tenderness and guarding in the upper abdomen. Roentgenographic studies on this occasion demonstrated a prepyloric ulcer with marked pylorospasm.

Surgical therapy was advised and a subtotal gastrectomy was performed. A large benign gastric ulcer was found penetrating into the pancreas. In the distal portion of the pancreas two nodules, measuring 1·5 and 2·0 centimetres in diameter, were discovered and were excised. Frozen section examination suggested that these were benign islet-cell adenomas, but later study of the paraffin sections revealed the nodules to be low-grade carcinoma of the islet cells (Fig. 86). Blood sugar estimations were normal and at no time in this patient's illness was there evidence of hyperinsulinism.

The immediate post-operative course was uneventful but in June, 1950, he was admitted to hospital with massive haematemesis. He was treated with blood replacement, sedation, antispasmodics and a careful diet, but abdominal pain persisted. The patient was operated upon again in September, 1950, at which time there was a gastric ulcer with liver penetration, a gastro-jejunal ulcer penetrating the anterior abdominal wall and gastro-colic and jejuno-colic fistulae. Involved tissue was resected and a new gastro-jejunostomy established.

His early post-operative course was satisfactory, but subsequently fistulae recurred, abdominal pain became troublesome and his nutritional status deteriorated despite the later establishment of a feeding jejunostomy. He died in July, 1951, following a massive haemorrhage, three years following his initial symptoms and 14 months after his first operative procedure.

At necropsy a marginal ulcer and multiple intestinal fistulae were found. The Zollinger-Ellison syndrome was not established at that time, and a meticulous examination of the pancreas was, unfortunately, not carried out.

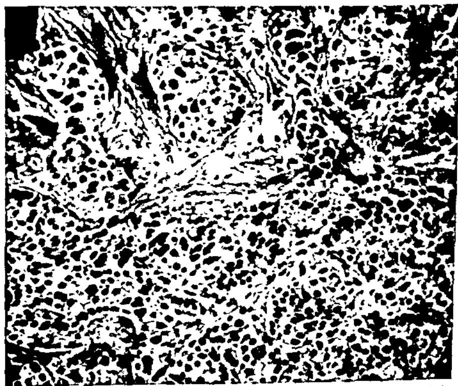


Fig. 86.—Photomicrograph from Case 5 illustrating low-grade carcinoma of the islets of Langerhans (×600).

The fulminating progression of the ulcer diathesis in this syndrome, and the failure of repeated surgical procedures to prevent complications are typical

features in the majority of cases. Ideally, treatment should depend upon a knowledge of the aetiology of the ulcer. Unfortunately, despite a mass of clinical and experimental data, we still do not understand the intricate relationship between enzymatic acid-digestion and tissue resistance underlying the cause of the Zollinger-Ellison ulcer, or for that matter, any other peptic ulcer. It appears certain, however, that gastric hypersecretion and hyperacidity play an important role in the aetiology of ulceration in the Zollinger-Ellison syndrome. Surgical therapy must therefore be directed in an effort to render the patient achlorhydric, and radical gastric resection, even total gastrectomy, has been recommended to achieve this purpose.

DISCUSSION

Hyperinsulinism

In the surgical treatment of hyperinsulinism, we believe that subtotal pancreatectomy has replaced enucleation as the procedure of choice for a solitary adenoma in the body, neck or tail of the pancreas. Left hemi-pancreatectomy can be readily performed in most instances with a very small operative risk. Non-palpable adenomas which might produce a recurrence of the hyperinsulinism, unsuspected malignancy or questionably malignant tumours are managed best by this procedure.

Recurrence of the hypoglycaemic syndrome following an original excision of a benign solitary adenoma with relief of symptoms is a rare occurrence. In the comprehensive series reviewed by Howard, Moss and Rhoads (1950) only four patients had a recurrence of symptoms which had initially been relieved. This was due to a second adenoma in two instances with early recurrence, and to adenomatosis and a probable carcinoma in the remaining patients. Another case is recorded (Eskelund, 1953) of a patient with relief of hyperinsulinism for 7½ years following excision of an apparently benign islet-cell adenoma from the head of the pancreas. At re-operation for recurrence of symptoms, malignant islet-cell tumours were removed from the body of the pancreas, but the outcome was fatal and at necropsy hepatic metastases were discovered.

The third patient in our report is believed to be a unique case with a remission of almost nine years after enucleation of a benign solitary islet-cell adenoma, followed by a recurrence of symptoms due to multiple adenomas which have been relieved by subtotal pancreatectomy. This patient remains well at the present time almost two years post-operatively.

Enucleation is the procedure of choice for an islet-cell adenoma in the head of the pancreas.

Encapsulation is not a *sine qua non* of a benign islet-cell adenoma nor does lack of a well-defined capsule imply that the lesion is necessarily malignant. The presence of metastases may occasionally be the only way to differentiate some of the borderline malignant tumours from frank carcinoma. Although the histological features of these questionably malignant tumours indicate their classification as "low-grade carcinomas", their benign clinical course following removal suggests they might be labelled more optimistically as "questionably benign".

Several authors have recently expressed doubt that islet-cell hyperplasia is a cause of hyperinsulinism (Breidahl, Priestley and Rynearson, 1955; Warren and Cattell, 1959). We believe that on rare occasions in patients with an increased

production of insulin the only pathological lesion that can be detected is hyperplasia or hypertrophy of the islet cells. Several instances are reported in Howard's series (Howard, Moss and Rhoads, 1950) and Campbell (1958) mentioned a case. Very recently we learned of a patient in whom distal pancreatectomy failed to relieve hyperinsulinism (Thal, 1959). Histological sections revealed hyperplasia of the islet cells. The disease was uncontrolled by steroid therapy, and subsequently a successful total pancreatectomy was carried out with satisfactory relief of the hyperinsulinism. Unfortunately in the fourth patient in our report, despite the clinical features and operative and pathological findings suggesting hyperinsulinism due to hyperplasia, with an abruptly terminated post-operative course, and the absence of a necropsy examination, conclusive evidence for this diagnosis is lacking.

Islet-cell hyperplasia is a rare cause of hyperinsulinism in infants and young children (McQuarrie, 1954; Douglas, 1959). Pancreatic exploration and resection should not be performed in this age group unless intensive investigation and lack of response to steroid therapy has eliminated the possibility of idiopathic hypoglycaemia (Kinsbourne and Woolf, 1959).

Zollinger-Ellison syndrome

The co-existence of an islet-cell tumour and peptic ulcer in patients exhibiting the Zollinger-Ellison syndrome does not appear to be a haphazard relationship. Unfortunately, experience has indicated that attempts to treat the ulcer by excision of the islet-cell tumour are unsuccessful in most instances. The ulcer diathesis appears to continue even in those patients in whom the tumour has been completely removed, unless a simultaneous operative procedure for the ulcer is performed (Zollinger and McPherson, 1958).

The endocrine implications of this syndrome are a fascinating aspect. Although the ulcer diathesis in not a proven function of either the islet-cell or other endocrine lesion, the frequent association with multiple endocrine tumours and the occasional familial tendency suggests that the syndrome may be part of a large, poorly understood pathological entity having a genetic or constitutional basis.

A very severe ulcer process may exist without an islet-cell or other endocrine tumour, and the Zollinger-Ellison syndrome may eventually prove to be only a segment of peptic ulcer disease. Unfortunately, not enough attention has been paid to parietal cell counts and similar forms of investigation in these patients.

The surgeon who may encounter the Zollinger-Ellison syndrome must base his management of this problen on the limited clinical experience available at present. An awareness of the lesion should be developed, particularly in patients with a severe ulcer, multiple ulcers, ulcer in an atypical location or a stomal ulcer. Whenever surgical therapy for peptic ulcer is undertaken the pancreas must be carefully explored, and if an islet-cell tumour is discovered it should be resected whenever feasible. Resection of the tumour should be performed for the neoplasm *per se* and not in the expectation that this procedure alone will cure the ulcer.

The discovery of an islet-cell tumour also serves as a warning that the ulcer diathesis may be virulent and require radical surgical measures. This initial radical approach undertaken early in the disease may prevent multiple operative procedures and late complications. We favour a radical subtotal gastrectomy combined

with vagotomy in an effort to render the patient achlorhydric, and would reserve total gastrectomy for those patients in whom it becomes apparent that a lesser procedure will not alleviate the threat of a fatal outcome.

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BIBLIOGRAPHY AND REFERENCES

Allan, F. N. (1958). Quoted by Marshall, S. F. *S. Clin. N. Amer.*, **38**, 775.
Banting, F. G., and Best, C. H. (1922). *J. Lab. clin. Med.*, **7**, 251.
Bickerstaff, E. R., Dodge, O. G., Gourevitch, A., and Hearn, G. W. (1955). *Brit. med. J.*, **2**, 997.
Breidahl, H. D., Priestley, J. T., and Rynearson, E. H. (1955). *Ann. Surg.*, **142**, 698.
Campbell, W. R. (1958). *Canad. med. Ass. J.*, **79**, 760.
Conn, J. W. and Seltzer H. S. (1955). *Amer. J. Med.*, **19**, 460.
Davey, P. W. (1959). Personal communication.
Douglas, D. M. (1959). *Arch. Dis. Childh.*, **34**, 171.
Duff, G. L., and Murray, E. G. D. (1942). *Amer. J. med. Sci.*, **203**, 437.
Ellison, E. H. (1959). Personal communication.
— Abrams, J. S., and Smith, D. J. (1959). *Amer. J. Surg.*, **97**, 17.
Eskelund, V. (1953). *Acta path. microbiol. scand.*, **33**, 113.
Garland, H. (1957). *Brit. med. J.*, **2**, 969.
Graham, R. (1929). Quoted by Howland, G., Campbell, W. R., Maltby, E. J. and Robinson, W. L. *J. Amer. med. Ass.*, **93**, 674.
Harris, S. (1924). *J. Amer. med. Ass.*, **83**, 729.
Herxheimer, G. (1926). *Klin. Wschr.*, **5**, 2299.
Howard, J. M., Moss, N. H., and Rhoads, J. E. (1950). *Int. Abstr. Surg.*, **90**, 417.
Kinsbourne, M., and Woolf, L. I. (1959). *Arch. Dis. Childh.*, **34**, 166.
Langerhans, P. (1944). Quoted by Whipple, A. O. *Surgery*, **16**, 289.
MacKenzie, W. C., and Norvell, S. T. Jnr. (1960). *J. R. Coll. Surg. Edin.*, **5**, 191.
— — Matthews, B. L., and Shnitka, T. K. (1958). *Canad. J. Surg.*, **2**, 6.
Mayo, H. W. Jnr., and Enerson, D. M. (1958). *Surgery*, **44**, 91.
Mayo, W. J. (1927). Quoted by Wilder, R. N., Allan, F. N., Power, M. H., and Robertson, H. E. *J. Amer. med. Ass.*, **89**, 348.
McQuarrie, I. (1954) *Amer. J. Dis. Child.*, **87**, 399.
Miller, D. R., Bolinger, R. E., and Friesen, S. R. (1959). *Ann. Surg.*, **150**, 684.
Minkowski, O. (1893). *Arch. ex. Path. Pharmak.*, **31**, 85.
Nicholls, A. G. (1902). *J. med. Res.*, **8**, 385.
Oberhelman, H. A. Jnr., Nelson, T. S., and Dragstedt, L. R. (1958). *Arch. Surg.*, **77**, 402.
Pease, G. L. (1947). Quoted by Lopez-Kruger, R., and Dockerty, M. B. *Surg. Gynec. Obstet.*, **85**, 495.
Priestley, J. T., Comfort, M. W., and Radcliffe, J. (1944). *Ann. Surg.*, **119**, 211.
Schafer, E. S. (1895). *Lancet*, **2**, 321.
Shaw, R. C. (1956). *Brit. J. Surg.*, **43**, 579.
Smith, M. (1959). *Brit. J. Surg.*, **47**, 155.
Somogyi, M. (1959). *Amer. J. Med.*, **26**, 192.
Summerskill, W. H. J. (1959). *Lancet*, **1**, 120.
Thal, A. (1959). Personal communication.
Warren, K. W., and Cattell, R. B. (1959). *New Engl. J. Med.*, **261**, 387.
Warren, S. (1926). *Amer. J. Path.*, **2**, 335.
Wermer, P. (1954). *Amer. J. Med.*, **16**, 363.
Whipple, A. O. (1944). *Surgery*, **16**, 289.
Zollinger, R. M., and Ellison, E. H. (1955). *Ann. Surg.*, **142**, 709.
— and McPherson, R. C. (1958). *Amer. J. Surg.*, **95**, 359.

SELECTED ABSTRACTS

Pancreatic surgery

WARREN and CATTELL (1959) discussed pancreatic surgery. They stated that the diagnosis of pancreatic heterotope should be borne in mind when radiological examination reveals a small smooth filling defect in the gastric antrum, pylorus or first part of the duodenum. Symptoms may be minimal. In the treatment of the condition limited excision is sufficient. Annular pancreas is often undetected on radiological examination and even on surgical exploration. Drey records that a correct diagnosis of annular pancreas was made pre-operatively in 14 of 62 cases. The degree of duodenal atresia determines the symptoms. The chief complications are duodenal obstruction, peptic ulceration, pancreatitis and obstruction of the biliary tract. Division of the pancreatic ring is a dangerous surgical procedure. It is better to by-pass the defect by means of duodeno-jejunostomy in infants and gastro-enterostomy with vagotomy in adults. The presence of acute pancreatitis should always be suspected in a patient who complains of severe pain in the upper part of the abdomen. Confirmation of the diagnosis may be obtained by determining the serum amylase and lipase, the blood sugar and the haemoglobin value. The initial treatment is medical unless the diagnosis is in doubt. Immediate operation is indicated, however, if the condition is complicated by pancreatic sepsis and abscess formation. Although cortisone should not be prescribed indiscriminately one must not hesitate to administer the drug in cases of severe illness due to pancreatic necrosis. In a review contributed by Bockus a mortality rate of only 1·2 per cent resulted from the use of medical treatment during the early stage of the disease. Pancreatitis may occur after subtotal gastrectomy or operations upon the biliary tract. The disease may result from direct trauma to the pancreas and vigorous manipulation of the sphincter of Oddi. Treatment consists in Miller-Abbott intubation, the administration of antibiotics and the restoration of fluid and electrolytic balance. Intrapancreatic obstruction is usually present in cases of chronic relapsing pancreatitis. If possible the site of the obstruction should be determined without resort to pancreatography, for acute pancreatitis may ensue when this method of diagnosis is employed. If chronic relapsing pancreatitis is accompanied by biliary disease the latter condition should receive primary attention. Subsequently various operations may be performed for the relief of intrapancreatic obstruction. The operations include transduodenal exploration and dilatation of the ducts of Wirsung and Santorini, pancreatico-duodenal resection, distal pancreatectomy and pancreatico-gastrostomy or pancreatico-jejunostomy. Chronic alcoholism and narcotic addiction may jeopardize the patient's chances of recovery. As for the surgery of pancreatic cyst, although there is a trend towards the use of internal drainage it is preferable to carry out external drainage when the cyst is infected, when no communication can be detected between the cyst and a major pancreatic duct and when the prognosis is poor. Drainage by means of a de Pezzer catheter is preferred to marsupialization. In the diagnosis of hyperinsulinism due to islet-cell adenoma glucose-tolerance curves are of less value than blood-sugar determinations after prolonged fasting. Patients with this disorder may be subject to attacks of convulsions. In these circumstances degeneration of the nervous system may ensue if diagnosis and treatment are delayed. Occasionally islet-cell tumours are associated with peptic ulceration. This syndrome is characterized by the formation of multiple tumours in the pancreas, with a tendency for malignant changes to develop. With reference to the diagnosis of carcinoma of the pancreas, in a series of 102 patients loss of weight was recorded in 96 per cent of cases. Jaundice was present in 75 per cent of cases, and this sign was observed in nearly all cases of carcinoma of the head of the gland. Diarrhoea occurred in less than half the number of patients and thrombophlebitis was rarely observed.

Relation of pancreatic ducts to the islets of Langerhans

YANG and HUNTER (1959) discussed the relation between the islets of Langerhans and the ducts and acini of the pancreas. In a necropsy specimen of pancreatic tissue the authors found a focus of proliferated duct epithelium with an arrangement similar to

that of the islets. Many capillaries were observed in this area. No granules were detected in the cystoplasm of the epithelial cells. Serial sections of other specimens of pancreas showed well-formed ducts within the islets. There was direct continuity between the islets and a number of small pancreatic ducts. It was concluded that, as the result of the proliferation of duct epithelium, the ducts had been transformed into islet tissue. Laguesse has examined pancreatic tissue derived from embryonic sheep and has demonstrated areas of primitive gland structure in which the cells proliferate to form protruding loops. Tubules and loops constitute primary islands which may persist. According to Pearce the islands of Langerhans of the human embryo originate from the proliferated cells of the primitive secreting tubules. Kelly and other observers have noted islets connected to ducts in the human embryonic pancreas, but some investigators deny the existence of these connexions. Hard states that, in the rat, the majority of embryonic islets originate from the pancreatic tubules. Soon after birth there is a considerable increase in the formation of islets and in the majority of cases the islets are derived from the secretory-duct system at the base of the acini. A few islets develop from the larger ducts. Various stimuli, such as insulin injections, neoplastic disease and starvation, produce an increase in the number and size of the islets.

Pancreatic islet-cell hyperplasia

Malabsorption and jejunal ulceration due to gastric hypersecretion

SUMMERSKILL (1959) described a case of malabsorption and jejunal ulceration associated with gastric hypersecretion and islet-cell hyperplasia of the pancreas. The patient was a man, aged 35 years, who suffered from attacks of epigastric pain before meals. Pain was relieved by food and antacids. The clinical manifestations included loss of weight, diarrhoea, steatorrhoea and recurrent gastro-intestinal haemorrhage. At laparotomy the proximal part of the jejunum was found to be inflamed and thickened. The diseased intestine was resected and pathological examination showed that the resected specimen contained several chronic peptic ulcers. As the symptoms persisted the case was investigated radiologically. A large peptic ulcer of the jejunum was detected. Gastric analysis revealed gross hypersecretion with large amounts of pepsin and free hydrochloric acid. It was considered that the increased gastric secretion had led to peptic ulceration of the jejunum, steatorrhoea, diarrhoea and inactivation of trypsin. The findings were compatible with the Zollinger-Ellison syndrome. Gastrectomy and splenectomy were performed, the tail of the pancreas and the diseased portions of the duodenum and jejunum were removed, and the jejunum was anastomosed to the oesophagus. Although the excised pancreatic tissue showed islet-cell hyperplasia there was no evidence of adenoma. Increased *alpha*-cell activity was observed, but the *beta* cells were normal. After the operation the acid-pepsin secretion was abolished. A barium meal examination revealed diminished motility of the intestines, and the steatorrhoea pattern was no longer present.

Spontaneous hyperinsulinism

DOUGLAS (1959) gave an account of a male infant, aged 8 months, with spontaneous hyperinsulinism due to benign hyperplasia of the islet cells. There was a history of convulsions at the age of 7 weeks, with recurrence of the fits about once a week. Usually the fits occurred in the morning before the first feed. At the onset of a fit the blood-sugar level ranged from 32 to 42 milligrams per cent. It was considered that the infant was suffering from an islet-cell tumour of the pancreas. Laparotomy was performed and two-thirds of the pancreas was removed. Thereafter the blood-sugar values reached normal levels. On histological investigation of the resected specimen islet-cell hyperplasia was observed, but there was no evidence of a neoplasm. Later on, although the fits were controlled, some mental retardation was apparent. The author adds that no similar case has been recorded in the British literature. Admittedly no neoplasm was detected, yet the findings were consistent with Whipple's criteria for the diagnosis of a functioning islet-cell tumour. It is unlikely that a minute adenoma still exists in the remaining third of the pancreas, for during the course of 5 years after the operation there has been no evidence of hypoglycaemia.

Hyperinsulinism

Diabetogenic effect

According to SOMOGYI (1959) carbohydrate tolerance is often impaired in cases of hyperinsulinism due to islet-cell tumours of the pancreas. The response to glucose-tolerance tests may resemble that of diabetes mellitus, and sometimes the level of the blood sugar may show extreme fluctuations. In addition, a transitory diabetic condition may develop after removal of the tumour. Sevringhaus believes that the diabetic-like glucose tolerance is probably attributable to overfilling of the glycogen stores after the administration of food to offset hypoglycaemic reactions, but Somogyi stresses the importance of the diabetogenic effect of hypoglycaemia which results from excessive insulin action. With the recurrent stress of hypoglycaemia the insulin-opposing factors gain ascendency, so that hyperglycaemia develops despite hyperinsulinism. During the hyperglycaemic phase overactivity of the adrenal-pituitary system subsides and insulin action again predominates. The term, adrenaline diabetes, is applicable to the transitory post-operative diabetes and the diminished carbohydrate tolerance associated with hyperinsulinism. Insulin injections for non-diabetic disorders may give rise to artificial hyperinsulinism. Changes in the carbohydrate metabolism resemble those observed in organic hyperinsulinism. Transitory diabetes occurs after discontinuation of the injections. Odin points out that the diabetogenic effect is directly proportional to the dose of insulin and to the duration of treatment. In view of the author's experiments on alimentary hyperglycaemia, it is concluded that the abnormal hyperglycaemic intervals in the condition of artificial hyperinsulinism are initiated by hypoglycaemia and not by lack of function of the rested pancreas.

Islet-cell tumours of the pancreas

SMITH (1959) presented three case reports on islet-cell tumours of the pancreas. The first report concerns a woman, aged 58 years, with a history of attacks of confusion and slurred speech. During the course of an attack the fasting blood sugar was 32 milligrams per cent. A glucose-tolerance test showed low readings. At operation an insulin-secreting islet-cell tumour, 1·5 centimetres in diameter, was removed from the pancreas. Subsequently the fasting blood sugar was 110 milligrams per cent and no further attacks were recorded. The second patient was a woman, aged 49 years, who experienced attacks of stupor. After blood-sugar tests laparotomy was performed and a reddish-purple nodule was removed from the pancreas. Post-operatively the blood sugar showed an increase from 82 to 160 milligrams per cent. With regard to the third patient, a woman aged 43 years, the symptoms resembled those of dementia with epilepsy. In this case the symptoms were relieved after the removal of three nodules from the pancreas. Smith pointed out that the pancreatic tumour associated with spontaneous hypoglycaemia is usually a benign adenoma. In 12 per cent of cases the lesions are multiple. Insidious in onset, the disease usually affects middle-aged patients. Recurrent bouts of fainting or abnormal behavour coincide with the need for food. Symptoms include anxiety, altered speech or vision, restlessness and convulsions. Disturbance of the autonomic nervous system leads to nausea, sweating, palpitations and tachycardia. Differential diagnosis is required from psychiatric conditions. Surgical exploration is indicated if the blood-sugar level during an attack is less than 50 milligrams per cent and the attack is relieved by glucose therapy. Thorough palpation of the pancreas is required. Access is facilitated by dividing the peritoneum along the inferior border of the gland and mobilizing the second part of the duodenum. If no tumour is found it is advisable to resect the left half of the gland. Whereas good results are to be expected after excision of an adenoma the outlook is likely to be poor in cases of malignant disease or diffuse hypertrophy of the islet tissue.

Organic hyperinsulinism

Insulin sensitivity

MONICO and his colleagues (1959) discussed insulin sensitivity in organic hyperinsulinism and the diagnosis of insulinoma. A six-minute insulin test described both by Anderson and by Fribourg in 1954 has been useful in determining the sensitivity of diabetic

patients to the hormone. It has greater value, however, in indicating excessive administration of insulin to patients who have no hypoglycaemic symptoms but are receiving more than their physiological requirements. Such chronic exposure to excessive insulin progressively diminishes sensitivity to the hormone, a reversible tendency corrected by reducing the dosage. The consistency of this finding suggested that the same phenomenon might exist in patients with endogenous overproduction of insulin, such as occurs in insulinoma. The six-minute test was therefore applied to four such patients. Insulin, freed from its hyperglycaemic factor and given intravenously, acts very rapidly and, after 20 seconds, there often occurs a steep fall in venous glucose, which can be observed during the six-minute period. Six cases are described. The first was a man with temporo-occipital headache and paraesthesia. A standard insulin sensitivity test suggested normal responsiveness, but the six-minute test showed complete absence to responsiveness. A diagnosis of insulinoma was made and at operation an insulin-producing islet-cell adenoma was resected. Recovery was immediate. The second case was a woman suffering from periodic syncope and convulsions of long duration, with hypoglycaemic episodes. Four years previously she had undergone laparotomy and subtotal gastrectomy A six-minute test demonstrated complete absence of sensitivity. Re-exploration revealed a gastro-jejunal fistula and multiple islet-cell adenomas, one suggestive of carcinoma. Resection ended the hypoglycaemic episodes. In two cases of functional hypoglycaemia the first showed an excessive sensitivity to insulin, the second a border-line response. Since the two patients with insulin-producing tumours showed complete absence of responsiveness, it seems that endogenous excess of the hormone has a sensitivity effect analogous to that produced by chronic excessive administration. Chronic hypoglycaemia, however, must be proved before a lack of sensitivity can be considered significant of organic over-production. Diagnosis of insulinoma is probably justified when the fasting true blood-glucose level is consistently below 50 milligrams per 100 millilitres, and 30 milligrams per 100 millilitres or less during an attack; when severe hypoglycaemia disappears on venous glucose administration; when intolerance to fasting exists. When symptoms are not typical, but hypoglycaemic episodes are nevertheless chronically recurrent, an absence of sensitivity seems to confirm the diagnosis of hyperinsulinism.

Idiopathic infantile hypoglycaemia

Kinsbourne and Woolf (1959) reported on idiopathic infantile hypoglycaemia affecting a female, aged 4 months. The patient was subject to uncontrollable generalized fits with no focal features. There was progressive mental deterioration. Physical examination revealed obesity, hypotonia of the limbs and diminished reflexes. The blood sugar during a fit was 35 milligrams per 100 millilitres. An intravenous injection of dextrose solution, 5 per cent, produced only a temporary increase in the amount of blood sugar. Hypoglycaemia was controlled, however, by ACTH and prednisolone therapy. The fits ceased, hypotonia was no longer observed and the gain in weight reached normal proportions. At the age of 10 months the child was more alert but her mental condition was still grossly retarded. Adrenaline and glucagon tolerance tests produced high blood-sugar levels. The true concentration of blood sugar was not reduced within 90 minutes by the oral ingestion of the amino acid, leucine. Blood and urine examination showed no evidence of galactosaemia. After the intradermal administration of insulin the initial blood-sugar response was normal. As the plasma-insulin level was found to be normal the hypoglycaemic state was considered to be idiopathic. In the circumstances laparotomy and pancreatic biopsy were contra-indicated.

Hypoglycaemia due to non-pancreatic mesodermal tumours

Case reports

Miller and his colleagues (1959) discussed hypoglycaemia in non-pancreatic mesodermal tumours. Large, slow-growing and encapsulated, these tumours resemble, microscopically, fibromas, mesotheliomas and sarcomas. In 10 cases, removal has produced relief of hypoglycaemic symptoms. Two more cases with fasting blood sugars of 10–20

milligrams per cent are presented. The first, a man of 73 years, was admitted with hypoglycaemic episodes. Blood sugar was 52 milligrams per cent. Eight years previously, a tumour in the space of Retzius had been removed. Laparotomy now revealed a large mass extending from the prostatic area to above the umbilicus; removal was contra-indicated. Pancreatic exploration showed a pulsating enlargement suggesting a vascular adenoma or splenic artery aneurysm. Subtotal pancreatomy and splenectomy were performed without relieving the hypoglycaemia. Acute colonic obstruction supervened, necessitating surgery. Sudden cardiac failure caused death. At necropsy, a tumour weighing 4,000 grammes was found to occupy the entire pelvis: the upper portion was necrotic. Sections obtained of the earlier tumour suggested a leiomyosarcoma, those from necropsy, a fibrosarcoma. It was finally regarded as a malignant mesodermal growth. The clinical history, absence of invasion and distant metastases at necropsy, were consistent with fibrous mesothelioma. The second patient, a woman of 59 years, presented with a history of "blackouts" two episodes of collapsing on rising from bed and convulsions diminished by taking food. Initial fasting blood sugar was 20 milligrams per cent. At laparotomy a nodule in the tail of the pancreas was first removed; subtotal pancreatomy and splenectomy were then performed. Ten days later, the hypoglycaemic seizures recurred. Further investigation suggested a mass involving the right diaphragm. Seizures persisted and fasting blood sugar was 17 and 10 milligrams per cent. At operation a circumscribed tumour was found arising from the central tendon of the diaphragm. This, with segments of the right lower lobe, was removed. Recovery was complete. Histologically, the tumour was extremely cellular with a striking lack of pattern but with some necrotic foci. It was diagnosed as a solitary fibrous mesothelioma. Fifteen of these tumours have been reported and many aetiological theories advanced. The association of the necrotic cystic areas with development of symptoms only after the tumour has assumed large proportions, suggests that a hypoglycaemic-producing substance with an action similar to insulin may be a breakdown product of tumour degeneration. Insulin activity assays, in both patients, support this theory.

Gastro-duodenal ulcers

Necropsy analysis with emphasis on associated endocrine disease

In a review of 20,000 consecutive necropsies Ellison, Abrams and Smith (1959) include 812 cases of active gastro-duodenal ulcer. Acute ulcers occurred more frequently in the stomach than in the duodenum, but the reverse was the case with chronic ulcers. Gastric and duodenal ulcers were more common among males than among females, Although chronic acid-peptic disease was rarely found in patients aged less than 30 years, almost 20 per cent of acute lesions were found in patients in this age group. Most gastric ulcers were found on the lesser curvature within 5 centimetres of the pyloric ring. In approximately 15 per cent of cases of chronic gastro-duodenal ulcer a gastric operation had been performed within six months of death. Haemorrhage and peritonitis were the primary causes of death in these cases. The incidence of diabetes mellitus was at least equal to that of the entire series. Acid-peptic disease of the oesophagus was present in nearly 10 per cent of cases of gastro-duodenal ulcer. Concomitant disease of the central nervous system was discovered in 37 per cent of cases of acute ulcer but in only 7 per cent of cases of chronic ulcer. Gastro-duodenal lesions were rarely associated with disease of the pituitary, thyroid and parathyroid glands, but there were 26 cases of islet-cell disease of the pancreas. Criteria for the diagnosis of nodular hyperplasia of the adrenal cortex included increase in the amount of intracellular lipoid material and pronounced thickening of the zona reticularis and fasciculata. Adrenal cortical hyperplasia occurred more often in cases of ulceration than in the entire series of necropsies. In view of this finding it is suggested that adrenal-gland activity is related to gastric secretion and that dysfunction of the gland is an important factor in the aetiology of acid-peptic disease. The authors refer to the cases of disease of the central nervous system and to Cushing's theory concerning the relation between intracranial lesions, parasympathetic activity and local ischaemia of the gastro-duodenal mucous membrane. It would appear that, in the presence

of intracranial disease, great difficulty would be encountered in distinguishing the "Cushing ulcer" from the ulcer due to stress.

REFERENCES

Douglas, D. M. (1959). *Arch. Dis. Childh.*, **34**, 171.
Ellison, E. H., Abrams, J. S., and Smith, D. J. (1959). *Amer. J. Surg.*, **97**, 17.
Kinsbourne, M., and Woolf, L. I. (1959). *Arch. Dis. Childh.*, **34**, 166.
Miller, D. R., Bolinger, R. E., Janigan, D., Crockett, J. E., and Friesen, S. R. (1959). *Ann. Surg.*, **150**, 684.
Monico, R. N, Anderson, G. E., and Kaulbach, M. (1959). *Metabolism*, **8**, 49.
Smith, M. (1959). *Brit. J. Surg.*, **47**, 155.
Somogyi, M. (1959). *Amer. J. Med.*, **26**, 192.
Summerskill, W. H. J. (1959). *Lancet*, **1**, 120.
Warren, K. W., and Cattell, R. B. (1959). *New Engl. J. Med.*, **261**, 280, 333, 387.
Yang, Y. H., and Hunter, W. C. (1959). *Arch. Path.*, **67**, 505.

MODERN METHODS OF TREATING RETINAL DETACHMENTS

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Operative treatment is indicated in the majority of cases of simple detachment of the retina, and a successful reposition can be obtained in about 65–70 per cent of all cases, both favourable and unfavourable. Cases of retinal detachment, especially those commencing above, are to be regarded as surgical emergencies and should be admitted to hospital without delay as the prognosis is, in general, much improved by early operation.

An accurate account of the patient's initial symptoms and a record of photopsia or of a positive scotoma, especially with regard to their position in the visual field, are of the utmost value as indicating the original position of the detachment and hence that of the retinal tear. The tear need not necessarily be found on that portion of the retina which is detached at the time of examination, as the subretinal fluid in relation to a detachment commencing above usually gravitates downwards; it follows that, in a detachment of some chronicity, the rent may be found on a flat or even apparently attached portion of the retina.

It is of the utmost importance to realize that retinal holes are very frequently multiple; therefore painstaking ophthalmoscopy, both direct and indirect, with accurate charting of all retinal defects found, is the pre-requisite for successful detachment surgery. Many find the binocular indirect ophthalmoscope first introduced by Schepens and using a + 20 D. aplanatic lens of especial value in this examination which should be undertaken with the patient comfortably supine on a couch or in bed. Full mydriasis is necessary for this fundus examination (atropine 1 per cent, or phenylephrine 10 per cent drops), and the meridian in which the hole lies is charted in a clock-like notation, the cornea being regarded as a clock face. Fortunately the majority of retinal holes are situated in front of the equator of the globe and are, therefore, readily accessible to surgery. Their distance behind the limbus on the appropriate meridian is calculated in the following way—in emmetropic eyes the ora serrata is taken as being 8 millimetres behind the limbus, in highly myopic eyes as 9 millimetres. This area of the fundus is visible to indirect ophthalmoscopy, but with direct ophthalmoscopy the anterior limit of view is some 2 millimetres behind the ora, though the latter can be brought into view by indenting the sclera over the region of the fundus periphery under examination. This indentation is made by a

specially shaped rod mounted on a thimble, which is worn on the middle finger of the left hand. The distance of the hole from the ora serrata is estimated in disc diameters, that is, units of 1·5 millimetres. Thus a hole calculated as being four disc diameters behind the ora in the centre of the supero-temporal quadrant of a highly myopic left eye is charted as being 15 millimetres behind the limbus in the 1.30 meridian.

The patient is put to bed with both eyes padded and in such a position that the retinal hole is in the most dependent part of the globe. The affected eye is kept under the effect of 1 per cent atropine drops once daily. From two to three days of postural rest with double padding are usually sufficient to show if a retinal detachment is going to respond well by becoming partially reposed and, in general, for those that do so diathermy should be considered as the operation of choice.

DIATHERMY

Diathermy which was introduced almost simultaneously by Larsson (1930) of Stockholm and Weve of Utrecht, was in general use for all types of cases in the next two decades, but began to be replaced by the scleral resection operation and its modifications at the close of the nineteen-forties.

The diathermy operation is too well known to need any description here except to mention that it is preferably performed under local anaesthesia, that accurate localization of the retinal hole or holes is very necessary, and that the diathermy applications should be applied solely over these defects so as to seclude them and not as isolated points remote from them unless it be to barrage off completely a diseased area of retina from ora to ora. It is also very important to avoid using too strong a current—rarely is it necessary to exceed 70 milliamperes for 7 seconds with the Keeler machine—as overheating of the globe may produce contraction of the vitreous gel and burns of the retina with consequent secondary tears. Diathermy applications should not be placed over an area of the choroid which is atrophic from disease or previous diathermy applications as no inflammatory response will be obtained.

Results

In a series of 191 eyes operated upon solely by diathermy in the years 1934–1948 —that is, before sclerectomy was employed in Great Britain—I obtained 62·3 per cent of successful repositions. Statistics relating to this group are shown in Table I.

Indications

In my experience diathermy is still indicated as the primary procedure in the following types of cases.

(1) *Detachments associated with a single tear*—usually U-shaped (*see* Fig. 94) or a localized area of multiple defects, usually rounded (*see* Fig. 92b), which respond well to posture. They do well with diathermy provided the diseased area of retina is close to the choroid at the time of operation, and air injection into the vitreous for those commencing above seems to improve the prognosis.

TABLE I

GENERAL STATISTICS OF 182 CASES (191 EYES) OPERATED ON BY DIATHERMY ONLY (1934–1948)

Average age	43·2 years	
		per cent.
Males	114	62 6
Females	68	37·4
Right eye	85	46·7
Left eye	65	35·7
Both eyes	32	17·6
Emmetropia or hypermetropia	67	35·1
Low myopia (0-5 D.)	38 } 110	19·9 } 57·6
Moderate myopia (5-10 D.)	37	19·4
High myopia (over 10 D.)	35	18·3
Aphakia	14	7·3
Repositions	119	62·3
Improvements (1948 only)	2	1·1
Failures	70	36·6

(2) *Detachments occasioned by the rupture of a retinal cyst* and detachments associated with peripheral dialyses (*see* Fig. 96a, b) not exceeding 10 millimetres in the long axis all do well with diathermy provided the detachment is not of too great chronicity, as shown by the presence of striae retinae, or the dialysis too large, with its edge retracted into the vitreous chamber and with healthy vitreous gel behind it.

(3) *Unruptured retinal cysts* do very well with diathermy (*see* Fig. 95 a, b). Light surface applications are placed over the whole scleral surface area of the cyst with special attention to its inner (disc side) periphery. A single puncture is then made with a large diameter (1 millimetre) needle and all the contents evacuated by the use of a sucker.

(4) *Holes without detachment* (*see* Figs. 92a, 93a, 94) require careful watching and often I do not operate but if there are signs or symptoms of impending retinal detachment such as retinal haemorrhages in relation thereto or a small vitreous haemorrhage, an operculum being retracted into the vitreous or persisten photopsia then I think it wise to do so. Gentle surface diathermy, 60 milliamperes for 6 seconds with the Keeler machine over the diseased area and with no punctures, is all that is required. Light coagulation (*see* p. 327), however, is now supplanting diathermy for this type of case.

(5) *In general*, for retinal detachments which respond well to rest and double padding, diathermy should be considered as the operation of choice; for those that do not, sclerectomy will usually be indicated.

LAMELLAR SCLERAL RESECTION

The full-thickness scleral resection operation which was originally introduced by Leopold Müller (1903) of Vienna, was largely abandoned with the advent of the work of Gonin (1934) in the nineteen-twenties on the importance of retinal tears in the aetiology of simple detachment of the retina and the successes obtained by the relatively simple operative procedures—cautery puncture (*Gonin*) and diathermy (Larsson and Weve) which followed and aimed at the seclusion of these

retinal defects. The full-thickness operation was revived by Lindner (1933) for cases of retinal detachment with unfavourable prognosis, but this procedure is often made technically difficult by bulging of the choroid; moreover, as the operation is frequently performed upon failures after diathermy, which tends to weld the sclera and choroid at the same time as producing retino-choroidal adhesions, there is often difficulty in the separation of these membranes; consequently there is considerable danger of vitreous loss and choroidal haemorrhage —always serious complications in any case of retinal detachment. For these reasons the present author developed in 1949 the operation of lamellar scleral resection (Shapland, 1951a, b); here a thin film of the deepest scleral lamellae is left *in situ* along the whole length of the excised scleral strip; such lamellar resection is combined with chemical and if necessary with diathermy coagulation. The lamellar scleral resection which quickly replaced the perforating procedure of Müller and Lindner after 1950 was independently introduced by Paufique (1959) of France in that year.

Technical considerations

The operation of lamellar sclerectomy is preferably performed under general anaesthesia, as it is imperative to have the patient quite still and relaxed, whilst the operation may take from 1 to 1½ hours to perform. It has met with considerable and rapid success and as it is being performed in most centres all over the world needs no further description here. A few practical points, however, may well be mentioned.

The operation acts by producing a ridge projecting into the choroid and retina to which the latter may adhere, and any defects therein become secluded by a mild inflammatory reaction engendered in the choroid underlying the excised scleral strip by 3 per cent caustic potash (Shapland) or diathermy (Paufique). The sclerectomy should be centred on the main visible rent in the retina and of sufficient length to cover all the tears discovered. Should no defects have been found the patient's history must be the guide, the first sclerectomy being placed over the region where the detachment presumably commenced. Normally the anterior incision of the sclerectomy is placed 10 millimetres behind the limbus, the width depends on the state of the vitreous, the distance of the defects behind the ora serrata and the amount of subretinal fluid, whilst the length is usually half of the circumference of the globe, averaging about 30 millimetres. The width should not exceed 3 millimetres if the vitreous is healthy and the detachment shallow, but in cases with a degenerate and fluid vitreous with deep detachment the width may be made appreciably greater but I have not yet exceeded 6 millimetres. Evacuation of the subretinal fluid is effected by a catholysis puncture or punctures (2 milliamperes) through the area of the sclerectomy and over the site where the bulk of the subretinal fluid is lying. The inwardly projecting ridge is formed along the centre of the excised strip on tying off the scleral sutures, and any retinal holes which have been estimated to lie behind this should be dealt with by surface diathermy first but without evacuation of the subretinal fluid as it is technically difficult to perform a lamellar sclerectomy on a soft eye. For these more posterior holes it is possible to place the sclerectomy further back, especially in myopic

eyes and on the temporal side, but in my experience it is unwise to site the anterior incision more than 12 millimetres behind the limbus. I normally temporarily sever only one rectus muscle, but if the retinal tears are so situated that a sclerectomy of over 35 millimetres is required at one session it is necessary to resect two, but I prefer not to do more than this at one session as such severing deprives the eye of a not unimportant vascular supply. The longest sclerectomy I have performed at one session to date measured 50 millimetres. Should the retinal defects be widespread, affecting all quadrants of the globe and associated with considerable vitreous retraction, the operation of Schepens is indicated. Here a greater choroidal infolding is effected by the employment of an encircling polyethylene tube around the circumference of the globe in a complete lamellar sclerectomy. I would agree with Paufique (1959), however, who in his Bowman lecture stated "I believe, personally, that it is essential to retain a simple technique, reducing trauma to a minimum. The different improvements that people have wanted to introduce to bring about a greater choroidal folding such as those of Schepens or of Custodis seem rather complicated, and it does not appear for the moment that the statistics have been greatly improved by these techniques".

Finally, if and when all defects have been covered by the sclerectomy, I like to put a little light surface diathermy at the two extremities of the former, curving forwards to the ora serrata so as to seclude completely the diseased area of retina.

TABLE II

SCLERECTOMY RESULTS 1949–1954

Aetiology	*Number*	*Cured*		*Improved*		*Failure*	
			per cent		*per cent*		*per cent*
Total eyes	150	62	41·3	45	30·0	43	28·7
Lamellar resections	142	61	42·9	43	30·3	38	26·8
Full-thickness resections	8	1		2		5	
Previous diathermy	70	30	42·8	20	28·6	20	28·6
No previous diathermy	80	32	40·0	25	31·25	23	28·75
Aphakia following:							
Congenital cataract discission	11	3		3		5	
Extracapsular extraction	8	3		0		5	
Intracapsular extraction	3	1		0		2	
Others	4	1		2		1	
Total aphakia	26	8	30·8	5	19·2	13	50·0
High myopia (over 10 D.)	33	8		11		14	
Moderate myopia (5–10 D.)	23	14		3		6	
Low myopia (under 5 D.)	24	11		8		5	
Total myopia	80	33	41·25	22	27·5	25	31·25
Emmetropia and hypermetropia. Senile 10; cystic 9; traumatic 9; secondary tears 7; B.S.D. 4 (6 eyes) inflammatory 2; Eales' disease 1	44	21	47·7	18	40·9	5	11·4

Results

In my first series of 150 eyes operated upon between May 16, 1949, and the end of 1954—8 by the full-thickness operation and the remaining 142 by the lamellar method—I obtained 43 per cent of successful repositions by the latter operation. These statistics are shown in Table II.

These pioneer results were very gratifying as at that time the sclerectomy was only employed on desperate cases and those which were known to have a poor prognosis with the older operation.

Indications

With further experience I find it wise to do a lamellar sclerectomy as the primary procedure much more frequently and it is indicated in this respect in the following types of cases.

(1) *Senile detachments* occur chiefly in eyes which are hypermetropic, emmetropic or with only a low degree of myopia. They are usually associated with sclerosis of the retinal arteries, show multiple defects which are fortunately mainly peripheral but in an atrophic retina and are therefore particularly prone to secondary tears with the diathermy operation.

(2) *Detachments of considerable chronicity*, especially old-standing inferior detachments showing multiple striae retinae, also occur mainly in eyes with little or no appreciable refractive error. They are essentially detachments of the young, and peripheral cystic degeneration is apparently the underlying cause.

(3) *Detachments occurring in aphakia*, in general, have a poor prognosis whether operated upon by diathermy or by sclerectomy, but, in my experience, they do better with the latter operation and there is, in addition, a distinct tendency to obtain improvements. Thus the percentage of complete failures, which was 64·3 in the 1934–1948 diathermy series, had fallen to 50 for the 1949–1954 sclerectomy cases. Schepens (1951) has found that degenerative changes near the ora serrata are more than twice as frequent in aphakic as in phakic subjects, and he found that the average number of "breaks" in 79 eyes was 4·45 per eye in this situation. The operation of lamellar scleral resection, therefore, is especially indicated here as a mild but widespread choroidal reaction is engendered directly behind the ora serrata.

(4) *Detachments occurring in myopia*, especially those with multiple and widely-spaced rents in front of the equator of the globe, are the cases which most frequently need an initial diathermy for a rent lying behind the main defects and which are not possible to include in front of the choroidal infold.

(5) *Diathermy failures* are an important indication, the large majority exhibit secondary tears, but occasionally a mal-reposition results with retinal tension folds and in both these groups of cases a sclerectomy rather than a further diathermy is indicated. When the diathermy has been excessive and a sclerectomy performed subsequently within two months, as may well be necessary with a spreading detachment, the sclerotic may be found to be so necrotic in the diathermized area that, *faute de mieux*, a full-thickness scleral resection has to be performed, and most of my full-thickness scleral resections have been done on this account.

(6) *Detachments associated with retraction of the vitreous*, such as occurs after vitreous haemorrhage, however produced, and especially if recurrent as in Eales' disease, in old-standing detachments, in those associated with retinitis proliferans and again also in aphakia especially after vitreous loss are indicative of lamellar sclerectomy.

(7) *Traumatic detachments*, especially those following intra-ocular foreign bodies and those associated with large peripheral dialyses, seem to do better with sclerectomy rather than with diathermy, but if a dialysis much exceeds a quadrant of the globe in length and is associated with inversion of the retina and healthy vitreous gel behind it, the prognosis from any form of operation becomes very bad.

(8) Lastly, as has already been mentioned, sclerectomy is indicated in general for retinal detachments which do not respond well to rest and double padding, whilst diathermy should be considered the operation of choice in those that do so.

Custodis's operative technique

The operative technique employed by Custodis (1956) of Düsseldorf needs mention here. After careful localization of the retinal tear by the transillumination method using indirect ophthalmoscopy, light surface diathermy is placed over the area of the rent, and then a special plastic polyviol implant having elastic properties is sutured under increased pressure at the same spot on the sclera, the implant being stretched first and then clamped in place by two or three mattress sutures of supramit. By producing a localized depression in the globe, the sclera and choroid are approximated to the diseased area of the retina and—what is of considerable interest—without any puncture for the evacuation of the subretinal fluid, the retinal hole becomes secluded and a cure of the detachment achieved.

THE VITREOUS IMPLANT

That degenerative changes in the vitreous body play an important part in the aetiology of simple detachment of the retina has been increasingly recognized during the past decade, though, in reality, this is no new thought, as it was first suggested by Leber as long ago as 1882 and later stressed by Gonin, Lindner and von Sallman. Indeed, the development of the various forms of the sclerectomy operation has been due to a tacit understanding of the importance of vitreous contraction and detachment in the causation of retinal separation, but it was Shafer (1956) of New York who in 1955 introduced the injection of human vitreous as an adjunct in the treatment of retinal detachment. The term "vitreous implant" is perhaps unfortunate as it is, of course, impossible to introduce into an eye without damage a tissue as delicate as the vitreous body. In actual practice a liquid vitreous aspirate is injected into the affected eye under pressure, and the effect of the liquid, which should have retained as far as possible the physical and chemical properties of normal vitreous, will be to increase the volume of the vitreous in the recipient eye and to force the retina into contact with the choroidal reactions however produced.

The donor eye

The donor eye is an enucleated human eye preferably removed within six hours of death. Immediately after removal the eye is placed in a penicillin and streptomycin suspension in sterile liquid paraffin (500,000 units penicillin, 500,000 units streptomycin, 5,000 grammes sterile liquid paraffin) where it remains for two hours. Then, with all aseptic precautions, the eye is removed from its container, rinsed in Ringer's solution, and a culture taken from the limbus and bulbar conjunctiva, after which it is placed in a glass bottle containing sterile liquid paraffin and stored in a refrigerator at 4°C.

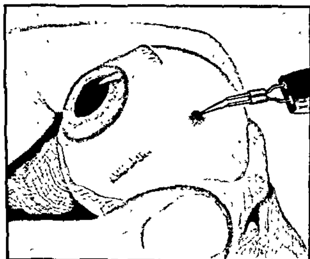


FIG. 87.—Cautery opening into donor eye. (*By courtesy of the Editor of the Transactions of the Ophthalmological Society of the United Kingdom.*)

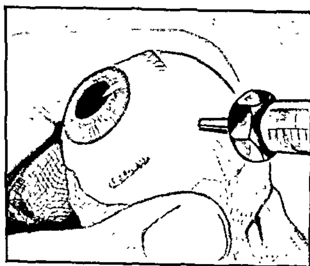


FIG. 88.—Aspiration of vitreous from donor eye. (*By courtesy of the Editor of the Transactions of the Ophthalmological Society of the United Kingdom.*)

Operative technique

The recipient eye is prepared for the vitreous injection, before any surface diathermy or other operative procedure has been undertaken for the retinal detachment, by making a small vertical opening in the conjunctiva and Tenon's

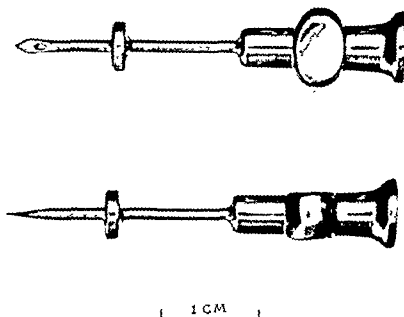


FIG. 89.—Vitreous implant needle (Shapland). (*By courtesy of the Editor of the Transactions of the Ophthalmological Society of the United Kingdom.*)

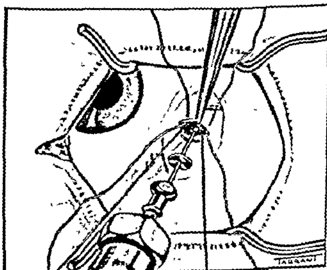


FIG. 90.—Injection of vitreous into recipient eye. (*By courtesy of the Editor of the Transactions of the Ophthalmological Society of the United Kingdom.*)

capsule 7 millimetres behind the limbus in the infero-temporal quadrant just below the insertion of the external rectus. The exposed sclera is cleaned and a small incision some 3 millimetres long, centred at 7 millimetres behind the limbus and parallel to the meridian at that point, is made with a Graefe knife just down to the pars plana of the ciliary body. A mattress suture of 00 white silk or plastic thread, doubly armed with Grieshaber 81/10 needles, is inserted across the small incision and the two threads in the base of the incision withdrawn with a scleral hook, the two loops so formed enable the assistant to separate the lips of the little wound at the time of the vitreous injection. The detachment operation, whether diathermy or scleral resection or a combination of both, is now proceeded with up to the stage of evacuation of the subretinal fluid.

The surgeon now changes over to a second trolley which contains the donor eye and a separate set of instruments. The cadaver eye is well rinsed in sterile normal saline solution so as to remove all paraffin globules and then held firmly in a large gauze swab in the left hand. The sclera is cleaned at a point some 14 millimetres behind the limbus and between any two recti. A cautery at dull red heat is now used to make an opening at this site, circular in shape, about 3 millimetres in diameter and shelving more deeply towards its centre, the cautery being applied intermittently until the choroid and retina are just perforated (Fig. 87). The opening should be of just sufficient size to accommodate the nozzle of a 2 cubic centimetre record syringe, which is now applied to the opening and with firm pressure on the globe with the fingers and thumb of the left hand and suction on the plunger of the syringe with the right, as much as 2 cubic centimetres of vitreous can be aspirated (Fig. 88)*. A special needle of 18 British Standard Gauge has been made to my design by C. Davis Keeler which has the advantage of not only a sharp point but of a cutting edge on each side of this so that it slips easily through the small incision in the recipient's eye, and it also has a stop 12 millimetres therefrom so that the needle cannot be inserted too far (Fig. 89). This is now placed on the nozzle of the syringe and the surgeon returns to the recipient eye to make provision for the evacuation of the subretinal fluid—this I do with a catholysis current of 2 milliamperes using a 0·5 millimetre diameter needle over the site where the main bulk of the subretinal fluid is lying. It is very important that there should be an obvious free flow of subretinal fluid before the vitreous is injected.

The vitreous aspirate is now planted into the recipient eye by inserting the 18-gauge needle through the little opening previously made in the sclera and directing it towards the centre of the globe. The eye being soft at this stage, the lower lip of the incision is supported by the assistant making traction on the lower loop of the mattress suture whilst the surgeon supports the upper lip with a pair of Jayle's forceps (Fig. 90). The vitreous is slowly injected until the eye becomes

* In taking the vitreous aspirate from the donor eye I now employ the vitreous implant needle instead of applying the nozzle of the record syringe to the globe as originally described. The needle is inserted towards the centre of the globe through an elliptical area at the equator sterilized by a cautery at dull red heat—it is unusual to obtain more than 2 cubic centimetres of vitreous aspirate and I use the same needle for the injection into the recipient eye so as to avoid losing any aspirate.

Operative technique

The recipient eye is prepared for the vitreous injection, before any surface diathermy or other operative procedure has been undertaken for the retinal detachment, by making a small vertical opening in the conjunctiva and Tenon's

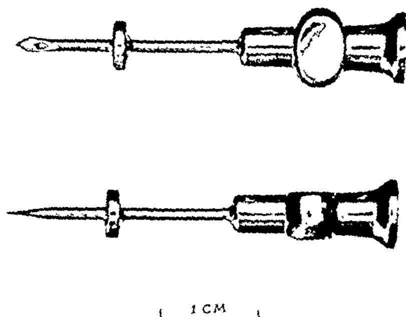


FIG. 89.—Vitreous implant needle (Shapland). (*By courtesy of the Editor of the Transactions of the Ophthalmological Society of the United Kingdom.*)

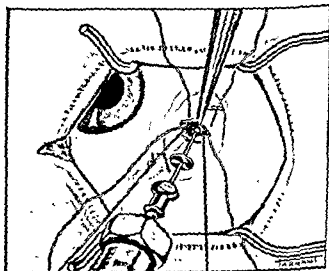


FIG. 90.—Injection of vitreous into recipient eye. (*By courtesy of the Editor of the Transactions of the Ophthalmological Society of the United Kingdom.*)

or hypermetropic eyes, these latter were mainly traumatic or inflammatory detachments. Twenty-two of these cases were blind in the fellow eye from previous retinal detachments and were, therefore, to be regarded as desperate cases, and indeed, I usually only employ the vitreous implant as a last resort after more orthodox detachment surgery—diathermy or lamellar scleral resection—has failed. I have, however, often combined the vitreous implant with other surgical procedures at the same operative session—9 times with diathermy, 6 with a lamellar sclerectomy, on 3 occasions with light coagulation, twice with a catholysis puncture over the retinal hole and once with an embedded polyethylene tube. I have now employed multiple vitreous implants in 5 cases, 5 separate injections in one case, 3 in a second and 2 in the remaining three, making a total of 46 implants to the end of 1959.

With regard to results 6 of the 37 cases were cured, 3 of the 11 aphakic detachments, 2 of the 18 myopic detachments and 1 of the inflammatory detachments in a hypermetropic eye. Although a temporary improvement in a retinal detachment is quite frequently seen following a vitreous implant it is rarely maintained for long unless the retina is completely replaced and although a further 6 cases do appear to have derived some permanent benefit from this procedure—1 aphakic, 2 myopic and 3 detachments in emmetropic eyes—the rest must be classed as failures.

Indications

In my experience the type of case which does best with the vitreous implant is a *subtotal detachment in which no definite unsealed retinal hole can be found*, indeed one in which a collection of subretinal fluid appears to have been trapped and has failed to become absorbed. At the time of the vitreous injection it is most important to puncture over the approximate centre of this loculus and to be sure of a free flow of subretinal fluid before injecting the vitreous aspirate.

The vitreous implant, therefore, would appear to have a small but definite place in the treatment of the more serious cases of retinal detachment that is, myopic, senile and aphakic detachments which have not responded to orthodox surgery and it is also worth trying in those cases showing vitreous traction bands. In my experience to date it is, rather surprisingly, the aphakic detachments which have responded the best.

LIGHT COAGULATION

That affections of vision can result from looking at the sun has been known from the earliest times and to this day every eclipse brings its little harvest of damaged maculae for which the appropriate name of eclipse blindness has been given. The solar radiations in these circumstances, both visible and infra-red, are brought to a focus on the macula by optical refraction, absorbed by the retinal pigment epithelium and the pigment of the choroid, and there degraded into heat. The resulting inflammatory reaction in the choroid and retina tends to weld these two membranes together. The experimental production of radiational chorio-retinal burns dates from the pioneer work of Czerny (1867) who concentrated sunlight on the eyes of several species of animals. His researches were followed by a number

quite firm and a gush of subretinal fluid can usually be seen escaping from the site of the catholysis puncture; firm pressure is maintained on the plunger of the syringe for two minutes to complete the evacuation of this fluid. The needle is held *in situ* while the assistant releases the loop of the mattress suture and makes half of a surgeon's knot—this he then ties off tightly as the surgeon withdraws the needle.

It is of interest to note that if the donor eye be now opened a much more compact vitreous is found remaining in the anterior portion of the globe and if the nozzle of the 2 cubic centimetre record syringe is applied to this it will not become aspirated into the syringe on making suction but will adhere to the nozzle and it, together with the retina and sometimes the lens as well, can all be withdrawn from the eye on the nozzle of the syringe.

Use of lyophilized vitreous

Paufique advocates the use of lyophilized vitreous, which he claims has properties identical with those of fresh vitreous and has the great advantage that it can be kept for a very long time in the form of a powder. To use it again it is sufficient to dissolve the powder in a corresponding quantity of warm distilled water after which a liquid is obtained having the same appearance and consistence as the normal fresh vitreous obtained by Shafer's technique.

Complications

It is important that the donor eye should be quite fresh, and used not longer than 24 hours after death. In two cases in which I used vitreous from eyes which had been kept for four days—both of these were early cases, my first and fourth —each after receiving second injections reacted violently with a panophthalmitis occurring in the first and a low-grade endophthalmitis in the second. At that time it was not clear whether this was an infective or allergic process but as both responded to intensive local and systemic antibiotic therapy, they presumably were infective in origin. Shafer, in September, 1958, assured me that he had met with no allergic reactions with subsequent vitreous implants, and since then I have employed multiple implants on three further cases—one receiving five, another three and the third two with no untoward reactions, but in all these three latter cases the donor material was under 24 hours old.

Complications of this procedure have been few and, apart from the two cases of endophthalmitis, not serious. There were three cases of secondary glaucoma and all occurred in aphakics; one lasted from the time of the implant for three weeks but eventually responded to Diamox systemically and pilocarpine locally; in the remaining two the raised tension appeared on the fourth day in one and on the sixth day in the other and both responded to Diamox, 250 milligrams four hourly within three days. Curiously enough two of these three cases were cured so a fleeting secondary glaucoma is certainly not of bad import.

Results

Between August 13, 1956 and December 31, 1959, I have performed a vitreous implant on 37 cases, 30 males and 7 females. Eighteen of these were myopic detachments, 11 aphakic detachments whilst the remaining 8 occurred in emmetropic

atmospheres when cold. It emits rays between 350 and 1,000 Mu.; thus the ultra-violet and infra-red ends of the spectrum are cut out hence avoiding injury to the cornea from the former and to the lens from the latter. As with direct solar radiation these rays only produce an effect where they are absorbed and this is normally by the pigment epithelium of the retina, the pigment in the choroid and that of the iris, and any lesion resulting therefrom may be assumed to be thermal in nature. The retina, if detached, does not absorb enough light to become coagulated, but if it is within 1–2 D. of the pigment epithelium and choroid it becomes involved in the inflammatory reaction engendered in the latter, and adhesions form between them.

Technique

In describing the technique of light coagulation the figures in parentheses refer to the key beneath Fig. 91. The image of the light source is formed in the image field diaphragm (8) by means of a lens system. A second image is formed on the fundus of the patient by means of an angled plane mirror (12) in the ophthalmoscope, the parallel light rays being then subjected to optical refraction by the eye of the patient. The image on the fundus is observed through an aperture in this mirror. When the current is turned on a perforation diaphragm permits only about 2 per cent of the total light beam to pass through. This contains two circles with fine perforations which form an image on the cornea of the patient's eye. At the centre of these circles a weakly illuminated image of the image field diaphragm is formed on the retina and this is directed by the surgeon on to the site to be coägulated. A release knob (14) in the handle of the ophthalmoscope is now pressed, the perforation diaphragm is pivoted out of the beam path, intense light comes through and coagulation takes place. Simultaneously a filter passes across the aperture in the ophthalmoscope mirror to protect the eye of the observer and prevent dazzle, thus the coagulation can be watched taking place. The intensity of the light is regulated by two multi-stage switches (23 and 25) and the amount of light getting through can be altered by an iris diaphragm actuated by a lever (29). The multi-stage switch for normal load is used for selecting the radiation strength in four stages during examination and coagulation, but intermediate settings can be selected continuously with the aid of the iris diaphragm. Should the radiation strength be inadequate for the desired coagulation effect with normal load, then the selector switch (24) is set to overload (red dot) and the multi-stage switch for overload (25) is set to the required value. The higher light intensity, however, of the lamp only becomes available on operating the release knob (14) in the ophthalmoscope handle (15). The area of the fundus to be coagulated is regulated by a milled wheel which selects the appropriate image field diaphragm (8) which vary in size from 6°, through 4·5°, 3°, 1·5° to 0·5°. For the emmetropic eye the diameter of the coagulation surface on the retina varies from 1·8 millimetres for the largest to 0·15 millimetre for the smallest opening. Thus both the size and intensity of coagulation can be controlled within fairly wide limits.

The optical equipment of the light coagulator is mounted in the optical beam director (28) which is mobile when the machine is in use, but should be

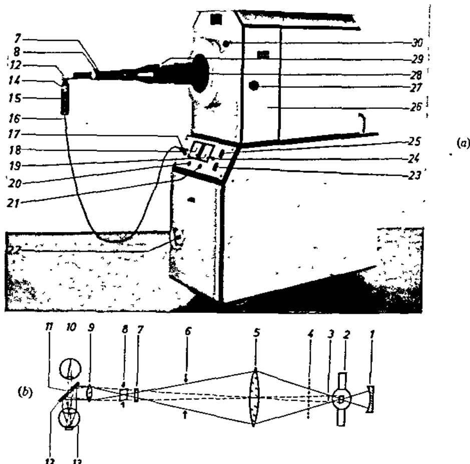


FIG. 91.—Zeiss light coagulator: (*a*) outer structure of the coagulator; (*b*) beam path in the coagulator.

1. Concave mirror
2. Lamp
3. Point diaphragm
4. Perforation diaphragm
5. Condenser
6. Iris diaphragm
7. Filter disc
8. Image field diaphragm
9. Objective
10. Eye of physician
11. Mirror apertures
12. Eye mirror
13. Eye of patient
14. Release knob
15. Handle
16. Cable
17. Cable connexion
18. Ammeter
19. Voltmeter
20. Switch-off key
21. Switch-on key
22. Protective switch
23. Multi-stage switch for normal load
24. Selector switch
25. Multi-stage switch for overload
26. Door
27. Door handle
28. Optical beam director
29. Lever for iris diaphragm
30. Locking lever

of others using both sunlight or the carbon arc concentrated by a lens, a mirror or a telescopic system. The practical application of light coagulation, however, we owe to the brilliant researches of Meyer-Schwickerath (1954) of Essen and the optical firm of Zeiss who together have developed a practical light-coagulation apparatus (Fig. 91).

The light coagulator requires a direct current of 380 volts for its light source which consists of a *Xenon high-pressure lamp* which operates at a pressure of 20

first described to the Ophthalmological Society of the United Kingdom in 1932 (Shapland, 1932). In these a detachment reaching up to the macula in one eye may occasionally be associated with an open dialysis at the ora serrata in its fellow but without an appreciable detachment. All these three types of cases are suitable for light coagulation.

(5) *Macular holes:* true holes at the macula are rare but the appearance of a hole in this situation is not uncommon, especially following contusion injuries to the eye or when the retina is tenuous, detached and the macular area involved. True holes at the macula without detachment or with only very slight elevation are ideal for secluding by this method using a small aperture (3 degrees) in the diaphragm and exposures of from $\frac{1}{10}$ to $\frac{1}{4}$ second to their periphery.

(6) *Zones of equatorial degeneration* which usually show band-shaped pigmentation, interlacing white lines and to which the vitreous is always adherent with the consequent danger of the formation of horse-shoe rents and also widespread peripheral cystic retinal degeneration are both indications for prophylactic light coagulation.

(7) *Small peripheral retinal cysts* can be sealed off by a barrage of light coagulation done from ora to ora in normal retina around the posterior border of the cyst.

PROPHYLACTIC TREATMENT OF RETINAL DETACHMENT

Since retinal detachment is only a stage in a slow process of degeneration of the eye, most commonly myopic or senile, and as at the present time no known method for the prevention of the invariable vitreous alterations is available, preventive operative treatment must necessarily be confined to the retina and there is no doubt that light coagulation is capable of extending the indications and possibilities in this direction. Thus it is now probably the safest method to employ for retinal tears with incipient detachment, for retinal holes without detachment and for secluding areas of retinal degeneration. Should a photo-coagulator not be available, however, light surface diathermy over the diseased area of retina and with no perforations of the sclera is quite satisfactory, and in a consecutive series of 630 cases of retinal detachment under my care from 1934 to the end of 1957, I used this method on 14 cases with success (Shapland, 1958).

Statistics show that some 20-25 per cent of retinal detachments are bilateral (23·1 per cent in my personal series of 731 cases operated upon between 1934 and 1959) (Shapland, 1960). Bilateral detachment is especially prone to occur in the young myope affected with the higher grades of this condition and in those who have been operated upon for a cataract, whether congenital or acquired. Aphakic detachments form some 8–10 per cent of all cases of retinal detachment (10·1 per cent in my 1934–1959 series), and they have notoriously a poor prognosis, especially those following discission of the lens for congenital or juvenile cataract. For the latter (Shapland, 1934) I found an incidence of 10·7 per cent after an average interval of 24·6 years following discission and some 50 per cent were bilateral. Following lens extraction of acquired cataract Paufique (1959) is of the opinion that when one eye has been affected by a retinal detachment, the other eye has a 25 per cent chance of being similarly affected should the lens be extracted. The probability, he stated, becomes greater when the cataract is presenile, when there is an absence of hereditary factors and where there has been

immobilized by the locking lever (30) when the coagulator is not functioning. The handle of the ophthalmoscope can be rotated on its own axis and also pivoted around the axis of the optical beam director, thus it is possible to examine and treat all parts of the fundus normally visible to direct ophthalmoscopy. Finally, the whole apparatus is mounted on wheels and can thus be readily moved about the theatre.

In treating a patient by light coagulation the pupil should be fully dilated with atropine 1 per cent or phenylephrine 10 per cent, and the affected eye anaesthetized by 1 per cent pantocaine drops. For small areas requiring coagulation this usually suffices, but if more intense and extensive coagulation should be required at one session a retrobulbar injection of 2 cubic centimetres of 2 per cent lignocaine is advisable. A speculum is inserted and the eye turned in the required direction by forceps or a squint hook pressed gently into the fornix. The light is now focused on the area to be coagulated and the release knob pressed. The shutter is kept open until the required degree of coagulation is seen, the optimum time for this being from ½ to 1½ seconds, and if no satisfactory coagulation is obtained within this small period of time the light intensity should be increased. If the intensity is too weak, and requires an exposure of longer than 1½ seconds the heat is carried away by the choroidal blood vessels and an unsatisfactory reaction is produced. The optimum intensity for each case has to be selected by experiment and, in general, the intensity has to be increased for peripheral lesions, in the presence of opacities of the transparent media, for lightly pigmented fundi and in highly myopic eyes.

Indications

In the treatment of retinal detachment, therefore, light coagulation is limited by the necessity of having the diseased retina preferably flat against the pigment epithelium or not detached more than 1–2 D. therefrom at the time of coagulation. Hence it is indicated in the following types of cases.

(1) *Retinal detachments which have responded well to posture* and binocular bandage with the retinal hole or holes once again in contact with the choroid.

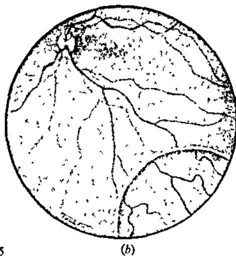
(2) *As an adjunct to diathermy or scleral resection*, for example, should a retinal rent be found post-operatively not to have been completely surrounded by diathermy reactions or lying on the disc side of the scleral infold and unsealed.

(3) *For peripheral detachments with open holes* which usually occur in young people and in the lower temporal quadrant. These detachments spread slowly, often show a tendency to become delimited by a zone of spontaneously formed retino-choroidal adhesions, and can readily be more firmly localized by a barrage of light coagulations placed along the adherent posterior edge of the detachment.

(4) *Retinal holes without detachment* (Figs. 92–97) which are generally of three types. First, U-shaped tears with operculum, the latter often retracted into the vitreous and to be regarded as impending detachments. Secondly, cases of myopia or retinal arteriosclerosis associated with peripheral retinal degeneration, usually of cystic type and showing multiple round or oval holes. Thirdly, small peripheral retinal dialyses. Apart from those due to direct trauma, these are most commonly seen in those interesting cases of bilateral symmetrical detachment of the retina usually occurring in young, non-myopic males and showing the features

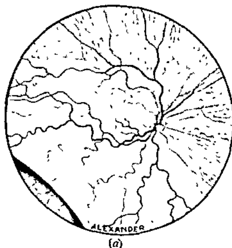


(a)

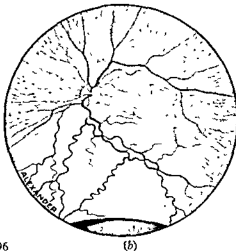


(b)

Fig. 95



(a)



(b)

Fig. 96

FIG. 95.—Bilateral symmetrical retinal cysts (a) right eye; (b) left eye.

FIG. 96.—Bilateral symmetrical detachment of the retina in relation to symmetrically placed dialyses infero-temporally (a) right eye; (b) left eye.

FIG. 97.—Massive cystic peripheral degeneration without detachment.

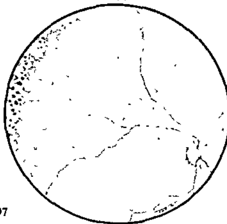
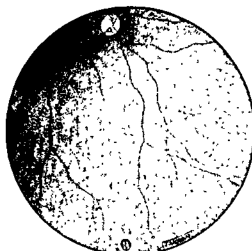


Fig. 97


(*a*)

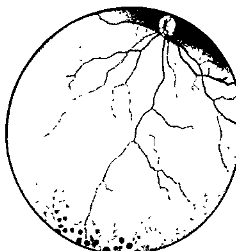
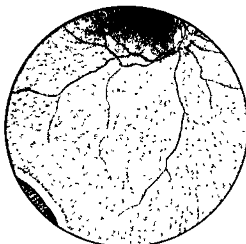

(*b*)

Fig. 92


(*a*)

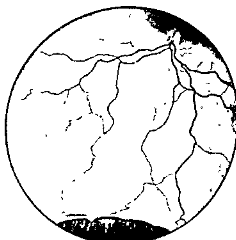

(*b*)

Fig. 93

Fig. 94

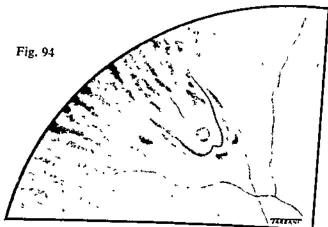


FIG. 92.—Round hole without detachment in (*a*) right eye and multiple holes with detachment in (*b*) left eye.

FIG. 93.—Bilateral symmetrical detachment with impending detachment in (*a*) right eye and extensive inferior detachment in (*b*) left eye.

FIG. 94.—U-shaped tear with impending detachment.

Czerny, V. (1867). *Wien Acad. Wissen.*, **56** (2), 409.
Gonin, J. (1934). *Le Décollement de la Rétine.* Lausanne; Librairie Payot.
Larsson, S. (1930). *Acta Ophthal., Kbh.*, **8**, 172.
Lindner, K. (1933). *Z. Augenheilk.*, **81**, 277.
Meyer-Schwickerath, G. (1954). *Proc. XVII int. Cong. Ophthal. (Montreal–New York)*, Sept. 1954.
Müller, L. (1903). *Klin. M. Augenheilk.*, **41**, 459.
Paufique, L. (1959). " Bowman Lecture." *Trans. ophthal. Soc. U.K.* **79**, 221.
Schepens, C. L. (1951). *Arch. Ophthal.*, **45**, 1.
Shafer, D. M. (1956). *N. Y. St. J. Med.*, **56**, 3,300.
Shapland, C. Dee (1932). *Trans. ophthal Soc. U.K.*, **52**, 181.
— (1934). *Ibid.*, **54**, 176.
— (1951a). *Proc. R. Soc. Med.*, **44**, 420.
— (1951b). *Trans. ophthal. Soc. U.K.*, **71**, 29.
— (1955). *Ibid.*, **75**, 405.
— (1958). *Proc. XVIII int. Cong. Ophthal. (Brussels)*, Sept. 1958. Vol. I, p. 1028.
— (1960). *Trans. ophthal. Soc. U.K.* In the press.
Weve, H. (1930). "Zur behandlung der Netzhautablösung mittels Diathermie." *Med. Tijdschr. Geneesk.*, **10**, 5.

SELECTED ABSTRACTS

"Medical" detachments of the retina

BONAMOUR (1959) discussed "medical" detachments of the retina. Although retinal detachment is an ocular disease, eminently surgical, a better understanding of the aetiology should provide a new therapeutic outlook to supplement surgery. There are retinal detachments without tears and tears without detachments. The existence of a tear is not enough to produce detachment; there must also exist a chorio-retinal lesion and probably a vitreous one. These "medical" detachments include: (1) exudative detachments; in those occurring in pregnancy the detachment is invariably bilateral, often of rapid evolution and at first, owing to gravity, affects the lower part of the fundus but may spread to engulf the macular area and indeed total detachment of both retinae, with blindness, may supervene. The same process is the cause of bilateral detachments appearing late in a retinitis due to malignant arterial hypertension or chronic albuminuric nephritis. Treatment should be directed to the cause. Once the general condition and retinitis are cured, the detachment resolves spontaneously. (2) A second category is associated with senile vascular degeneration and is probably related chiefly to choroidal sclerosis. Two types seen in chronic hypertensive arteriosclerosis are unaccompanied by tears and cannot be considered surgical. (*a*) These detachments occur in "central disciform exudative degeneration". The retina is raised on a thin liquid bed, which spreads laterally round the central lesion, but never reaches the periphery. Senile arteriosclerotic macular "pseudo-perforation" does not spread and is not complicated by peripheral detachments. Medical treatment and possibly radiotherapy are justified. (*b*) Retinal detachments accompanying choroidal lesions do not spread; they heal spontaneously when the choroidal lesion is healed. (3) A third category comprises traction detachments associated with retinitus proliferans. These are true complications, occurring in the last stages of retinal phlebitis, in the course of retinal angiomatosis or phakomatosis and as the final picture in diabetic retinitis. All justify medical treatment of the cause. (4) The fourth and most important category embraces acute uveitis with detachment and detachment with a uveal reaction. (*a*) The former constitutes the Vogt-Koyanagi-Harada syndrome, the aetiology of which is uncertain, but is undoubtedly of a viral nature. The detachment is usually an accompaniment of severe uveitis with intense iritis. Spontaneous cure is usual and often remarkably complete. (*b*) Detachments with uveal reactions are unilateral and present one or several tears. Even if surgical repair is necessary, medical treatment is essential before, during and after operation. In the aetiology, tuberculosis and all other infections may be responsible

loss of vitreous. At cataract surgery prophylaxis necessitates the avoidance of multiple needlings and capsulotomies for the congenital and juvenile types whilst in the adult loss of vitreous is to be avoided by care and complete akinesia, and post-operative iris prolapse by adequate suturing.

In the case of the young myope with detachment in one eye and degenerative retinal lesions in its fellow, prophylactic treatment should be undertaken by *photo-coagulation on the second eye so as to seclude all visible degenerative areas.* For the second type of case where there may well be a cataract in the fellow eye obscuring all view of the fundus, prophylactic surgery is much more debatable. Prior to cataract extraction Paufique advocates epichoroidal galvano-cauterization of the upper part of the sclera between the three and nine o'clock meridians in two to three rows, the anterior being 15 millimetres from the limbus and the posterior up to 20 millimetres.

It is thus most important in all cases of retinal detachment to examine the fundus of the fellow eye under full mydriasis, and in the absence of any retinal lesions likely to develop dangerously as regards hole formation to advise the patient to avoid such actions as are known to be harmful such as stooping, straining, lifting heavy weights or sudden jerky movements of the head and eyes. Strenuous sports should be given up especially by the young myope and boxing, which is especially dangerous in this respect, should be banned.

Barraquer (1958) advocated the operation of lamellar scleral resection as a prophylactic procedure for eyes with multiple retinal lesions especially if there has already been a detachment in the other eye. He is of the opinion that it is particularly indicated in myopic eyes from which the clear lens has been extracted for the correction of high myopia. By reducing the volume of the vitreous chamber, the scleral resection, he stated, eliminates the pendular movements of the vitreous thus decreasing the risk of a retinal detachment.

I have performed a lamellar sclerectomy only once as a prophylactic procedure and this was in a male myope, whose left eye had detached in 1947 and had been operated upon elsewhere without success, and whose right eye showed extensive peripheral cystic degeneration with multiple round and oval holes all along the temporal periphery. This intervention, in 1957, was successful and the retina has remained in place to date with full field and central vision 6/6 with correction (−4·5/−2·0 ax. 90°).

It is thus clear that the preventive treatment of retinal detachment is a most difficult subject requiring of the surgeon a wide experience and sound judgment. There is no doubt, however, that photo-coagulation has enlarged the scope of possibilities in this respect.

ACKNOWLEDGEMENTS

I am indebted to Mr. E. R. Alexander for Fig. 96 and to Mr. T. R. Tarrant of the Department of Medical Illustration of the Institute of Ophthalmology for the rest of the illustrations with the exception of Fig. 91 which is reproduced from the Carl Zeiss manual of operating instructions for their light coagulator.

REFERENCES

Barraquer, J. (1958). *Proc. XVIII int. Cong. Ophthal. (Brussels)*, Sept. 1958. Vol. 1, p. 1037.
Custodis, E. (1956). *Klin. Mbl. Augenheilk.*, **129**, 476.

Elevation of choroid by insertion of polyvinyl sponge

An experimental study

KAZDAN, HENDERSON and PARKHILL (1959) believe that implantation of polyvinyl sponge may be of value in the surgical treatment of retinal detachment. The authors base their belief upon studies of experiments in which the sponge was implanted into the eyes of a series of 27 dogs. In each case one eye served as a control. For the first eighteen operations the technique consisted in washing the sponge and then boiling the material in distilled water. Strips of the sponge were prepared and implanted into the anaesthetized animals. The strips were 3–5 millimetres wide and 5–23 millimetres in length. The material was inserted through two antero-posterior scratch incisions in the superior part of the sclera, and the choroid between the incisions was separated by means of a spatula. Paracentesis of the anterior chamber was performed in order to prevent an undue rise in intraocular pressure. The sponge was pulled into the suprachoroidal space by means of an iris repositor with a hole in the tip of the blade; then the scleral incisions were closed with black silk sutures and the conjunctiva was closed with catgut. Modified techniques were employed in the experiments on the remaining nine dogs. For instance in one eye the scleral incisions were made parallel to the limbus. In another eye a large piece of sponge was implanted near the posterior pole, thereby demonstrating the accessibility of this area. Healing was rapid in all cases. The light reflex was retained and the anterior chamber soon regained its normal depth. No visible elevations were produced by sponges which were 1·5 millimetres thick, but areas of the retina and choroid were raised by several of the thicker sponges. Elevations were detected even after a period of 59 weeks. Use of precompressed sponge was particularly effective in producing elevation of the choroid. After the animals were killed the eyes were removed, hardened in formalin and examined macroscopically and under the microscope. Four eyes showed a mass of tissue on the surface near the insertion of the superior rectus muscle. The findings included healed choroiditis in the vicinity of the sponge (7 dogs) and holes in the retina and choroid (11 dogs). The vitreous was normal in 21 of 27 cases. A vitreous haemorrhage had occurred in one case but at enucleation 50 weeks later it was evident that absorption had taken place. In four instances slender bands of vitreous were seen; the bands had taken origin at a hole in the retina. Detachment of the retina was not observed. Measurements of the implants showed a diminution in thickness of 30–85 per cent. An uncompressed sponge, 8 millimetres in thickness, was found to have caused a choroidal and retinal elevation of 3·5 millimetres. Microscopical examination of the implants showed acute inflammation and then foreign-body giant cells, fibrous tissue and blood vessels. Finally the sponge was occupied by mature fibrous tissue.

Scleral imbrication

SWAN (1959) stated that scleral imbrication has been used in the treatment of more than 100 cases of retinal detachment, with successful results in nearly 80 per cent of these cases. The operation consists in undermining the outer layers of the sclera and then overlapping them. As a result, there is pronounced flattening of the curvature of the globe in at least one quadrant. If the retinal disinsertion is localized to one quadrant the technique is as follows. An incision is made through the conjunctiva and Tenon's capsule in the equatorial region. The inferior nasal quadrant and the temporal half of the globe are exposed. Traction sutures are placed under the inferior and lateral rectus muscles. The scleral incision follows the curve of the globe and extends into the outer three-fourths of the scleral tissue. The deeper layers of the sclera and choroid are exposed over an area which extends from the ora serrata to a line situated well behind the equator. It is not necessary to employ preliminary placement of pins, for the retinal defect can be localized accurately by focal indentation of the sclera with forceps. Contraction and distortion are avoided by applying diathermy to areas in the surrounding sclera. Diathermy of the deeper layers of the sclera is effected by means of multiple applications of an extremely fine needle with a current of relatively high amperage. With this needle there is little or no heat damage to the surrounding tissues. The holes

as well as the more attenuated virus infections. Treatment is difficult. Diathermy-coagulation often seems to increase the exudative process. Operation indicated by a tear should be postponed until the detachment is "cold". When there is no tear, temporization is justified and lamellar resection only indicated to empty a persistent pocket. Sulphonamide therapy and chemotherapy are seldom effective except in tuberculosis. Intravenous cyanide of mercury is the classical treatment. Treatment with corticosteroid drugs and local radiotherapy have proved beneficial.

Traumatic retinal detachments and myopia

SÉDAN (1959) discussed traumatic retinal detachments and myopia. This follows a previous paper on the study of seven detachments of the retina wrongly diagnosed as traumatic. Among these seven cases which the author refused to impute to trauma and which survived from 3 to 24 months, were five patients with unilateral myopia which was moderate or severe, and two with lesser degrees of myopia. Research has produced detailed histories of eight detachments of incontestable traumatic origin which are considered here. Imputability of a detachment to trauma, either direct or by contrecoup, depends upon: (1) the definite existence of direct injury to the globe or its osseous surroundings. (2) The supervention (within 30 days) of the detachment upon the injury. (3) Equality, or part equality, between the condition of the fundus anteriorly on the injured and detached side and that on the non-injured and non-detached side. (4) The site of the retinal rent at the level of the ora (disinsertion). (5) The generally favourable operative result. Other cases, however, must not be rejected automatically but judged individually. Among the eight globes where the detachments were of proved traumatic origin, all presenting disinsertions, five were not myopic, two were feebly myopic and only one presented a myopia of 8-D. Its uninjured fellow, however, had a myopia of —14-D, divergent strabismus and amblyopia. Four of these detachments resulted from violent direct injury to the globe or its immediate neighbourhood; four from contrecoup from frontal cranial or temporo-occipital trauma. These findings suggest that absence of myopia in the eye with the detachment indicates a traumatic origin and are in agreement with the work of de Vincentiis of Naples in 1955 and Shapland in 1932.

Retinal separation

Exudative type

SUDARSKY (1959) described the development of Harada's disease in a female child, aged 8½ years. Signs of the disease were observed three weeks after an infection of the upper respiratory tract. Examination of the eyes revealed cells, flare in the anterior chamber, vitreous opacities, bullous retinal separation and retinal exudates. Pleocytosis was detected in the cerebrospinal fluid. From time to time the eyebrows and scalp hair showed white patches. Prednisone and other oral steroids were administered for more than three years, but signs of activity persisted. Increased activity with diminished vision occurred when steroid therapy was withdrawn. Side-effects of treatment included pronounced basophiloid changes and hirsutes of the face and trunk. Transient increase in intraocular pressure occurred during the early phase of the disease and secondary glaucoma became evident three years later. It was difficult to be certain whether glaucoma was directly associated with uveitis or whether the condition was secondary to prolonged administration of steroids. Although treatment failed to prevent the progress of chorioretinal atrophy there was a reduction in the severity of retinal exudation. Clarity of the media improved and useful central vision was maintained. Commenting on the case, Sudarsky states that Harada's disease, the Vogt-Koyanagi syndrome and sympathetic ophthalmia constitute variants of a single disease. Mitsui believes that in Harada's disease the uveitis is mainly confined to the posterior pole, whereas in the Vogt-Koyanagi syndrome uveitis is more severe and its distribution is generalized. As for the prognosis of Harada's disease, the outlook is less favourable in cases of pronounced elevation of the retina than in cases of flat detachment.

portion of the shaft is such that depression of the sclera may be accomplished over a limited area when only slight pressure is exerted.

Drainage of subretinal fluid

SCHWARTZ (1959) gives an account of various techniques for draining the subretinal fluid in cases of retinal detachment. Intravitreal injection of air, saline or vitreous constitutes an adjunct to drainage, but the injection must be made with special care when sclerotomy is employed. It should also be noted that the injection may give rise to strands in the vitreous. The multiple-pin technique allows slow emptying of the fluid and prevents the formation of traction folds. If any openings prove to be inadequate, other openings suffice for drainage. The technique should not be employed if the retinal elevation is less than three diopters. The pins are inserted round the affected area with quick stabs perpendicular to the scleral surface. Penetration is facilitated by the use of the diathermy current, but the current is turned off as soon as the sclera and choroid are pierced. The retina must not be exposed to the heat generated through the pins, and care must be taken to avoid perforating the vortex vein emissaria and the long posterior ciliary vessels. Drainage may be insufficient if the pins are short, if the fluid is too viscid or if the pins are inserted in an area where the quantity of fluid is minimal. It may be possible to verify the position of the pins by means of ophthalmoscopy. The pins are removed simultaneously after drainage. If a pin becomes dislodged prematurely it is advisable to remove the remaining pins immediately, for replacement of the dislodged pin is a hazardous procedure. When sclerotomy is employed correctly there is hardly any danger of causing retinal perforation with the electrode needle. The incision may be made either radial or parallel to the limbus. With the radial incision there is less risk of injuring an emissary vessel. Although use of this technique is effective in draining the subretinal fluid, complications such as retinal and vitreous prolapse may occur unless meticulous attention is paid to detail. The third technique consists in plunging an electrode through the sclera at several points. With this technique, however, the depth of the perforation cannot be evaluated by means of the ophthalmoscope. Moreover, if the first perforations precipitate the escape of subretinal fluid the subsequent perforations increase the hazard of retinal damage. Control by ophthalmoscopic observation is also difficult when a sharp punctum dilator is employed for perforating the sclera and choroid.

Re-operation after diathermy or scleral resection

Difficulties encountered

Discussing difficulties which may be encountered in re-operating after a diathermy operation or after scleral resection, OKAMURA, SCHEPENS and BROCKHURST (1959) refer to the oedematous condition of sclera treated with diathermy. Furthermore, the sclera may rupture or become adherent to scar tissue. On the other hand, after a scleral buckling operation the folded portion of the sclera is protected by a polyethylene tube and the danger of perforating the globe during re-operation is reduced because the orbital adhesions are relatively easy to dissect. Before perforation of the subretinal fluid the fundus must be examined with the ophthalmoscope. The sclera is incised in a meridional direction and a small portion of choroid is exposed. Subretinal fluid is released either in the vicinity of the new lamellar scleral resection or at a point situated posterior to the buckle. Perforation of the choroid is performed with a fine diathermy needle and the scleral incision is closed with a mattress suture. The existing scleral buckling may be made more extensive by replacing a partial tube with a circling tube. The appropriate sutures are removed and the tapered end of the circling tube is telescoped into the partial tube. A polyethylene tube is passed as a sleeve on the end of the circling tube and over the knot of a circling suture. Chloramphenicol solution is injected into the circling tube after the knot is tied. It may be necessary to continue the lamellar scleral resection round the globe and to bury the circling tube completely. Sometimes the circling tube must be shortened in order to produce a higher buckle. If retinal breaks are not adequately covered leaks may develop on the borders of the existing buckling.

made by the needle are considered to be of the correct depth as soon as the colour of the choroid is observed. A blunt-tipped electrode is applied to the base of the holes and a current of low amperage is employed in order to produce coagulation. The deeper layers of the sclera are incised and the choroid is opened carefully, thereby releasing the subretinal fluid. If the fluid is released before completion of the scleral flaps diathermy may result in choroidal detachment. The choroid and sclera under the flaps are infolded by applying a current of low amperage with a ball-type electrode. Massive choroidal detachment is produced, but at this stage the detachment is not detrimental. The incision is closed with chromic-gut mattress sutures. The anterior flap is tucked under the posterior flap, the deeper layers of the sclera and choroid are infolded, and the forward edge of the posterior flap is sutured to the sclera with fine radial sutures.

Scleral buckling operation

Use of accessory instrumentation

SUDARSKY and KATZIN (1959) described the use of accessory instrumentation for the scleral buckling operation. Special tube forceps may be employed for grasping the polyethylene tube without crushing or deforming the tubing. A groove on the instrument ensures control of the tube and mattress sutures. Shaped like a muscle hook, a tube clamp is of value for drawing the tube under the muscle. Globe repositors are aids for reducing proptosis, for gaining access to the posterior part of the globe and for application to the sclera of a very soft eye in order to increase the intraocular pressure, thereby facilitating insertion of the sutures. The concave surface of the instrument can be placed firmly on the cornea without injuring the tissues. The choroid pick, an extremely fine stainless-steel device, is useful during exposure of the choroidal hernia by dissection, and fluid expressors maintain the patency of the hernia during drainage of the fluid.

Scleral buckling operation with rolled scleral flap

ČAVKA (1959) described the use of scleral buckling and tucking in the surgical management of retinal detachment either with multiple tears or with large tears and disinsertion of the ora serrata. The operation may also be employed for pronounced cystoid degeneration, for multiple tears with high myopia and for large or multiple tears with adhesions of the vitreous to the retina. The technique consists in resection of a rectus muscle and incision of the sclera. A flap of the sclera is dissected to a depth which allows the choroidal pigment to become visible. The width of the flap may be increased from 4 to·5 millimetres when degenerative changes are found in several areas and when retinal detachment is associated with high myopia, atrophy and cystoid degeneration. Mattress sutures are inserted into the sclera, diathermy is applied to the detachment, the scleral flap is rolled into a tube and the sutures are tied over the rolled flap. Čavka adopted the technique in the treatment of three cases of retinal detachment. A large scleral tear was present in a patient with myopia and multiple tears were found in two patients with a history of retinal detachment due to trauma. Complete re-attachment of the retina occurred after the operation, with improvement in visual acuity and in the size of the visual field. A retinal fold was produced and the pressure exerted upon the choroid and retina was of value in relieving post-operative chorioretinitis in the vicinity of the tear. Flattening of the fold was complete within four weeks.

Use of fixation pick and scleral depressor

URRETS-ZAVALIA (1959) described a special instrument which can be employed as a scleral depressor, fixation pick and marker for retinal-detachment surgery. The instrument has a slender steel shaft bent at right angles near its extremity. The centre of the terminal platform carries a short-pointed process. Rotation of the eyeball is easily controlled by means of the point and a small indentation is made at the site where the coats of the eye are depressed. The relatively short handle ensures that less interference is encountered when direct ophthalmoscopy is employed, and the shape of the bent

MICTURITION DISORDERS ASSOCIATED WITH SPINA BIFIDA

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INTRODUCTION

Spina bifida and the allied neurogenic conditions constitute a group of diseases referred to collectively as congenital spinal palsy; they present many problems in treatment of the various skeletal deformities and abnormalities of vesical and rectal function. The management and treatment of this most difficult congenital deformity is a challenge to the surgical ingenuity and skill of the orthopaedic surgeon, neurosurgeon and urologist. The treatment demands at every stage the closest co-operation of all the members of the surgical team, and the numerous operative procedures required to produce the final result have to be carefully planned and staged and then performed with meticulous technique. No other congenital anomaly is associated with such a bizarre collection of deformities and symptoms: the treatment of each one may be long and tedious, fraught with many pitfalls and disappointments.

In no other congenital anomaly does the restoration of the normal physiological functions of the bladder and rectum play such an importat part. The various definitive orthopaedic procedures cannot be performed until treatment has been instituted to control, or alleviate, the distressing urinary and faecal incontinence. The challenge to a restoration of bladder function, and control of urinary incontinence has been met by the development of new and more specialized techniques, notably transurethral resection of the bladder neck, and diversion of the urinary flow by cutaneous ileo-ureterostomy. Experimental and clinical research has shown that this is not only a safe and satisfactory method to employ, but it has brought a merciful relief to the long and painful suffering of these unfortunate patients.

CONGENITAL SPINAL PALSY

The term congenital spinal palsy is one suggested by Ellison Nash to describe cases in which paraplegia resulted from spina bifida, sacral agenesis or other anomalies of the lower vertebrae. It is proposed to discuss some of these lesions before considering the treatment of micturition disturbances. Nash (1956) drew attention to the important fact that the child with congenital spinal palsy was becoming an increasing social problem. With the advent of the antibiotics and with the increased obstetric and paediatric care together with a higher standard of infant

In these circumstances the buckling must be widened. Re-application of diathermy is indicated if leakage is due to insufficient use of diathermy at the first operation. If additional scleral buckling is required a trap-door procedure is employed. Other procedures consist in using a second circling tube or a meridional tube placed under the existing circling tube. It is preferable to place the second circling tube posterior to the existing tube. A lamellar sclerectomy is performed, diathermy is applied to the bed of the resection, and 0000 non-absorbable mattress sutures are inserted. The second circling tube is placed under the mattress sutures and the circling suture is tied after the choroid is perforated. With regard to placement of the meridional tube, a lamellar resection is performed at right angles to the equatorial resection. Diathermy is applied and mattress sutures are employed for buckling in the short tube. After placement in the bed of the buckle the meridional tube is trimmed to the proper size. All sutures are tied when ophthalmoscopy reveals that the retina is approximated to the choroid.

Retinal detachment surgery

Results

MALBRÁN and MALBRÁN (1959) discussed the use of Schepens' method of indirect binocular ophthalmoscopy. In 1956, when the authors gave an account of a series of 85 cases of retinal detachment, the following groups were designated according to the severity of the disease: (1) subclinical detachments and tears without detachment, (2) uncomplicated detachments, usually of recent origin and reacting favourably to rest and bandaging, (3) detachments complicated by conditions such as pronounced myopia with chorio-retinal and vitreous degeneration. The third group included cases in which rest and surgery had failed to bring relief. In a further series of 101 patients fewer cases were assigned to group 2 and there were correspondingly more cases in group 3. Although this alteration in the grouping may have been due to chance some significance was attached to increased experience in pre-operative examination and to the good results which were obtained in apparently hopeless cases. When the two series were compared it was found that success was invariably achieved among patients in group 1. For group 2 the second series showed an increase in cures in the ratio 87:95, but for group 3 the ratio of improvement was 58:79 provided that cases of very advanced disease were omitted from consideration. As for technique, diathermy applications were controlled by the use of the indirect binocular ophthalmoscope. By this means accurate localization was ensured and there was less risk of applying diathermy to normal tissues. Damage to the conjunctiva was avoided by the local injection of physiological saline. The conjunctival incision was made at a point situated 1·5 centimetres from the sclero-corneal limbus. A myostat was used for muscle disinsertion. Two sutures in the tendon served as guides for subsequent re-insertion of the muscle. Adhesions and post-operative heterophoria were avoided by covering the sclerotomy area with a flap derived from Tenon's capsule. Surface diathermy was employed for evacuation puncture, but saline solution was injected into the vitreous chamber when insufficient fluid was evacuated.

REFERENCES

Bonamour, G. (1959). *Ann. Oculist., Paris*, **192**, 161.
Čavka, V. (1959). *Brit. J. Ophthal.*, **43**, 361.
Kazdan, M. S., Henderson, J. W., and Parkhill, Edith M. (1959). *Amer. J. Ophthal.*, **47**, 437.
Malbrán, J., and Malbrán, E. (1959). *Brit. J. Ophthal.*, **43**, 288.
Okamura, I. D., Schepens, C. L., and Brockhurst, R. J. (1959). *Arch. Ophthal.*, **62**, 445.
Schwartz, A. (1959). *Amer. J. Ophthal.*, **47**, 98.
Sédan, J. (1959), *Ann. Oculist., Paris*, **192**, 175.
Sudarsky, R. D. (1959). *Arch. Ophthal.*, **62**, 5.
— and Katzin, H. M. (1959). *Ibid.*, **62**, 503.
Swan, K. C. (1959). *Arch. Ophthal.*, **61**, 110.
Urrets-Zavalia, A. Jnr. (1959). *Arch. Ophthal.*, **62**, 97.

of these fibres which are involved. Thus the changes in bladder function will differ greatly, ranging from the automatic non-reflex bladder with its hypertrophied walls and bladder neck, gross trabeculation and varying amounts of residual urine, to the atonic thin-walled bladder, also trabeculated, but containing large quantities of residual urine. Unfortunately, in addition to the bladder lesion, there are associated pareses of the musculature of the lower limbs, of the perineum and of the external urinary sphincter. Dilatation of the upper urinary tract with ureteral reflux occurs if there is a large volume of residual urine in the bladder resulting from obstruction at the bladder neck or increase in sphincteric tone.



FIG. 98.—Sacral defects associated with meningocele which produced severe urinary obstruction terminating in death from uraemia.

Sacral agenesis

Sacral agenesis is another developmental anomaly which produces micturition disorders similar to those seen in spina bifida; and though relatively rare is worthy of more detailed consideration. Isolated cases of this condition have been reported and described by various writers, but the first comprehensive survey of collected cases was made by Freedman (1950) who added one personal case to the series. Innes Williams and Nixon (1957) reported eight personal cases, and classified the various degrees and types of sacral agenesis. Often a developmental abnormality of the rectum exists in association with sacral agenesis, but it can occur with normal rectal development. Rectal and urinary incontinence

welfare and nursing, infant mortality as a whole, and especially that from congenital spinal palsy, has fallen markedly. The associated increase in the birth rate, and therefore the relative increase in the number of children with congenital spinal palsy, has in turn led to increased survival of these deformed children as more are being brought for treatment. The majority of these children present with rectal and urinary incontinence in addition to the complicated skeletal deformities. In some cases there is also cerebral retardation, which in itself makes co-operation of the patient during treatment extremely difficult. Frequently these children are only seen late in the course of the disease, when sepsis has produced irreversible structural changes in the upper urinary tract making further treatment difficult, and at times impossible. It is regrettable that these children are brought for treatment at such a late stage because then little can be done for them apart from palliative treatment for the urinary and rectal symptoms.

Spina bifida

Spina bifida or myelodysplasia is a congenital defect of the vertebral column resulting from failure of fusion of the dorsal walls of the primitive neural tube. The defect may be situated in any part of the vertebral column, but it is most frequently found in varying degrees of severity in the lumbar and sacral regions. The most simple form of this condition is a spina bifida occulta in which there is a small bony defect in the lumbar region. The affected area is covered completely with skin, and the lesion is often only revealed and clinically appreciated on account of the characteristic dimpling and pigmentation over that area. Infrequently its presence is revealed solely by a small lipomatous pad of tissue, often pigmented, in the region of the spinal defect. Confirmation of this anomaly is obtained by radiological examination. Spina bifida occulta is a lesion found frequently and is usually unassociated with any symptoms or neurological signs; however, cases have been reported in which neurological and urological signs have occurred in later years, usually following a period of active growth. It has been suggested that as a result of the growth of the child traction has been exerted on the cord because the filum terminale is anchored in the sacral area.

Frequently the defect in the lumbar area is more extensive with protrusion of part of the meninges, or of the cord and its nerve roots thus producing a meningocele or a meningomyelocele (Figs. 98, 99, 100). The disability resulting from this defect varies with the extent of damage and degeneration of the cord and the nerve roots affected. Clinically the neurological signs resemble those seen in the cauda equina lesion which is frequently encountered in the adult, but are variable, differing markedly in apparently similar cases. Often, there is little loss of sensation even with the most severe neurological deformities. There is, however, always some abnormality of vesical or rectal function in addition to the various skeletal deformities.

Urological features

In cases with a moderate or severe defect, the urological problem is one of regulation and control of the varying degrees of incontinence. The neurological lesion has wide clinical and symptomatic variations, depending on whether the sensory or motor nerve fibres are affected, and also on the relative proportion

occur with this condition. In isolated cases, rectal control has been normal and mention will be made of this when the treatment of the urological symptoms is discussed.

The author has had personal experience of five cases of true sacral agenesis, the age incidence ranging from 2 to 60 years. All of the patients had the characteristic feature of one sacral vertebra which showed developmental abnormality and irregularity of contour (Fig. 101.) In a large proportion of these cases associated abnormalities of the lower lumbar vertebrae and skeletal system were present. Abnormality of gait is not a common symptom, though in one case in the series



FIG. 101.—Typical deformity of sacral agenesis.

personally reported it did occur and was associated with sensory loss in the perineum and medial side of the thigh. Atrophy of the muscles of the buttock produced a characteristic deformity of the natal cleft (Fig. 102,) and in addition there was wasting of the muscles of the lower limbs (Fig. 103.) Palpation and rectal examination reveals the bony defect in sacral agenesis; anterior and lateral radiographs of the pelvis and lumbar spine conclusively established the diagnosis (Figs. 104, 105.)

The urinary symptoms in sacral agenesis are in no way proportionate to the degree of bony deformity and range from partial to complete incontinence. In addition, the upper urinary tract may or may not be congenitally abnormal (Fig. 106), but there will be pathological changes resulting from neurogenic dysfunction of the lower urinary tract.



FIG. 99.—Sacral and lumbar defect associated with meningomyelocele and bilateral hydronephrosis with urinary incontinence. Improvement followed transurethral resection of bladder neck.



FIG. 100.—Photograph of child with thoracic and lumbar spina bifida. Urinary incontinence treated by ileocutaneous ureterostomy.



FIG. 104.—Lateral radiograph showing a bony defect in sacral agenesis.



FIG. 105.—Sacral agenesis showing sacral scoliosis.



FIG. 102.—Deformity of natal cleft due to developmental abnormality of the gluteal muscles with sacral agenesis.

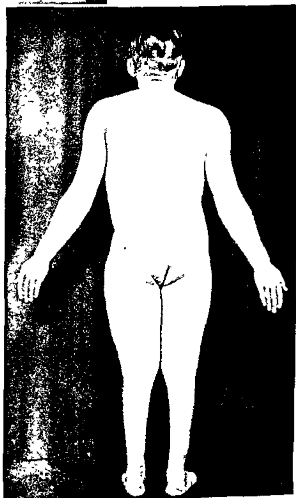


FIG. 103.—Photograph showing atrophy of the muscles of the lower limbs in sacral agenesis.

Disturbances of rectal function with rectal incontinence and absence of anal sensation are common findings, though in certain cases there is complete rectal continence which permits uretero-colic anastomosis to be utilized as a method of treatment of the urinary incontinence (Fig. 107).

The pathological anatomy of the nervous system in sacral agenesis is somewhat obscure there being only one necropsy report in the literature. Pugh described the necropsy findings in a girl aged 12 years who died with sacral agenesis, and his findings were similar to those seen at operation in one case in the personal series. It was noted that the cord was split unequally, irregularly and longitudinally, simulating the changes seen in diastematomyelia. It was flattened, but the nerve roots which emerged from its lateral margin appeared macroscopically normal. Minor degrees of sacral agenesis are compatible with a full and uneventful life, though the more severe lesions cause a considerable decrease in the survival rate.

ASSESSMENT OF METHODS OF TREATMENT

Several factors must be fully appreciated, and a critical assessment made before choosing any elective method of treatment. The wide variation of clinical manifestations in cases with apparently similar neurological lesions does not allow a definite classification of the type of treatment. The dysfunction of micturition varies not only with the age of the patient but also with the secondary changes that have occurred in the urinary tract as results of recurrent urinary infection and obstruction. Again critical assessment has to be made of the physical and mental capacity of these patients. The treatment also varies very markedly in the two sexes; urinary incontinence in the female presents a much more difficult and formidable problem of treatment than in the male. Operative or remedial treatment which can be carried out effectively and without risk in one case may be a highly dangerous or fatal procedure in another, and each case thus has to be assessed individually.

The aims of the urological treatment must be (1) to eliminate, or reduce the amount of residual urine, and (2) to correct, or improve the degree of urinary incontinence.

Before considering treatment it becomes obvious that there are three main groups of patients which must be considered. The first is the one in which there is complete urinary incontinence and absence of residual urine. The second and largest group comprises those with complete or intermittent urinary incontinence with varying amounts of residual urine. It should be noted that in this group there is often dilatation of the upper urinary tract and gross hypertrophy and trabeculation of the urinary bladder. The third group of cases is that in which there is retention of urine with overflow incontinence, the bladder often being grossly distended and sacculated, and with various degrees of dilatation of the upper urinary tract (Fig. 108.) It should be the primary aim of treatment in all these patients to correct the urinary incontinence and secondarily to abolish or reduce the amount of residual urine in the bladder, thereby minimizing attacks of recurrent urinary infection with the attendant dangers of damage to the upper urinary tract. Quite often, however, permanent structural changes have occurred in the bladder and



FIG. 106.—Sacral agenesis, vertebral anomalies. Intravenous pyelogram showing solitary hydronephrotic pelvic kidney on the right side.



FIG. 107.—Neurogenic dysfunction of the bladder due to sacral agenesis. Treated by ureterocolic anastomosis, pyelogram showing dilatation of the upper urinary tract.

to appreciate that unless carried out with proper technique, the findings may be misleading and fallacious. The various types of neurogenic dysfunction of the bladder can be classified into four well-defined groups each having a characteristic cystometrogram and symptomatology.

In the normal cystometrogram there is a gradual rise of intravesical pressure in response to filling with a desire to void occuring between 200 and 250 millilitres and with an urgent desire to void occurring at about 400 millilitres. At this stage there is a sharp rise in the intravesical pressure, voiding occurs, and the pressure returns to normal (Fig. 109.)

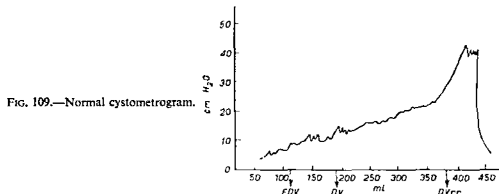


FIG. 109.—Normal cystometrogram.

Uninhibited neurogenic bladder

The cystometrogram pattern of uninhibited neurogenic bladder may be seen in cases where there is interference of supranuclear control from high cortical centres, or where there is súbtotal destruction of the spinal cord pathways. In both instances the sensory pathway from the bladder is intact. The characteristic of this cystometrogram is that micturition is imperative on filling of the bladder and voiding is complete. After filling commences there is a strong desire to empty the bladder with increasingly active detrusor contractions which may continue after the patient has voided urine. There is, during the waking hours, central appreciation of the state of the bladder (Fig. 110.)

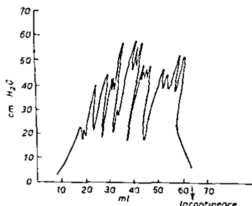


FIG. 110.—Cystometrogram of uninhibited neurogenic bladder.

the upper urinary tract, as a result of infection and back pressure phenomena, which prevent complete control of urinary infection.



FIG. 108.—Radiograph showing sacral agenesis, congenital dislocation of left hip, and neurogenic bladder with ureteral reflux.

INVESTIGATIONS

At this juncture it would be advantageous to mention the plan of investigation which is used in these children. Apart from the general physical examination and the intellectual and mental assessment, routine blood chemistry and blood urea estimation and full blood counts must be carried out. These children often show a microcytic and hypochromic type of anaemia. An intravenous pyelogram should be carried out whenever possible to estimate not only the function, but the configuration of the upper urinary tract and ureters. It is, of course, valueless in those cases in which there is elevation of the blood urea above 80 milligrams per 100 millilitres.

Cystometrography

An estimation of the residual urine should be made and if possible at the same time a cystogram should be performed. This latter investigation gives very useful information regarding the degree and type of obstruction which exists at the bladder neck, and reveals any alteration in contour of the bladder wall as a result of sacculation and the formation of diverticula. Cystometry and estimation of sphincteric pressure has given valuable information in certain cases. In small children, however, it is a difficult investigation to perform and it is important

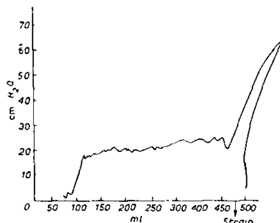


Fig. 112.—Cystometrogram of autonomous neurogenic bladder.

with many hundred millilitres of fluid without the patient experiencing any discomfort or bladder sensation or desire to void. Straining or suprapubic pressure does produce a very transitory rise in intravesical pressure, but never greater than 30 centimetres of water (Fig. 113).

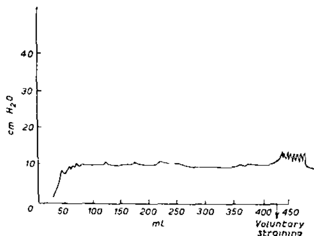


Fig. 113.—Cystometrogram of atonic neurogenic bladder.

TREATMENT

Having carried out the initial assessment of the patient and estimated the extent of the urinary tract lesion, it is necessary to plan the future stages of treatment for the individual case. Many methods have been used to treat the urinary symptoms each one having its relative advantages and applicability to certain types of case. It is proposed to discuss these critically with special reference to the various vesical lesions. The methods of treatment available in these cases vary from the simple re-education in bladder training to more complicated operative procedures such as ileal ureterostomy. It is often advantageous to use a combination of the various methods discussed below to alleviate the urinary incontinence.

Reflex neurogenic bladder

A reflex neurogenic bladder may result from disease or destruction of the cortex, of the spinal cord pathways, or from transection of the cord above the micturition centre in the sacral segment. The act of micturition is entirely reflex and precipitate; each act of voiding is complete, occurring at frequent intervals with complete absence of sensation in the bladder. The typical cystometrogram shows that there is a short quiescent interval while filling to 50–60 millilitres capacity, followed by immediate evacuation due to detrusor contraction. These rhythmical contractions occur without any sensation of fullness of the bladder or desire to void (Fig. 111).

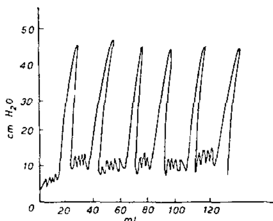


FIG. 111.—Cystometrogram of reflex neurogenic bladder.

Autonomous neurogenic bladder

Autonomous neurogenic bladder is the commonest type of neurogenic bladder and occurs in approximately 25 per cent of cases. It is seen in the nuclear or infranuclear lesions of the sacral segments or of the conus or cauda equina in which there is interruption of both the afferent and efferent fibres of the reflex micturition arc. Micturition is therefore involuntary and incomplete with absence of vesical sensation and is associated with residual urine. The typical cystometrogram shows a high filling pressure always over 10 centimetres of water. The bladder capacity can be normal, but it is usually greater than normal due to residual urine. Sensation to void is absent, and even with gross distension of the bladder, the patient is aware only of a vague feeling of distension in the pelvis. Coughing or straining causes an increase of intravesical pressure which falls rapidly (Fig. 112).

Atonic neurogenic bladder

An atonic neurogenic bladder is seen when the posterior sacral roots or spinal columns are affected, causing an interruption of the afferent fibres of the reflex arc. There is absence of reflex micturition and of sensation in the bladder; voluntary micturition is impossible. Residual urine is considerable, usually over 200 millilitres and emptying of the bladder is achieved only by overflow incontinence or by manual suprapubic pressure. The characteristic cystometrogram shows a flat tracing at a constant low pressure and it is possible to fill the bladder

materials, and with disposable plastic bags. This has helped the patient considerably, but it is, however, neither possible nor desirable to commit a small child to the portable urinal. Not only is it unpleasant and often unacceptable, but constant use produces ulceration of the prepuce and glans penis. Often ulceration of the urethra and external meatus also develops, and recurring attacks of sepsis are inevitably followed by fibrosis and stricture of the meatus.

Furthermore, the wearing of a portable urinal is cumbersome, and often prevents the fitting of orthopaedic appliances which could correct and control skeletal deformities. Though it is important to control urinary incontinence, the fact that the patient has to walk again must not be forgotten. Yet these appliances for the control of urinary incontinence have an inherent "safety" value in that they raise morale and have permitted many of these patients to travel by public and private transport and to take up, often for the first time, an occupation without the constant fear of urinary incontinence. It has enabled people with minor degrees of incontinence to undergo vocational training and to become useful members of society.

TRANSURETHRAL RESECTION OF THE BLADDER NECK

Transurethral resection of the bladder neck is not an operation to be undertaken indiscriminately, particularly in small children, even though improved miniature resectoscopes have made this technically possible; it is not a feasible procedure in a child under the age of two years. The operation is not without risk as in these children there is often very little tissue to be resected from the bladder neck, and there is the danger of fistula formation. This is especially so in the female where a vesico-vaginal fistula may result, while resection in the male can produce extravasation of urine and blood into the peri-prostatic tissues which results in infection and local abscess formation. Often the first attempt is unsuccessful and repeated resections have to be performed to establish adequate bladder drainage and to reduce the volume of residual urine.

The author has no enthusiasm for this method in small children, though it is often of great use in older children with the autonomous type of bladder. Dilatation of the female urethra to maximum calibre can also bring about considerable improvement in incontinence and a reduction in the amount of residual urine. The ease with which the female urethra can be dilated to a large calibre enables the operator to introduce larger instruments, thus permitting a more detailed inspection of the bladder neck and a more adequate resection. Emmett and Dunn (1946), who have had considerable experience with this method reported good results in only one third of a series of patients. The patients in whom the results were good had a complete return to normal micturition. Some degree of incontinence was present in the remaining patients, though they were considerably improved. In all the patients in this series there was a complete reduction of the volume of residual urine.

PLASTIC OPERATIONS ON THE BLADDER NECK

Considerable popularity has been given to plastic operations on the bladder neck in American literature, but the majority of surgeons in Great Britain have not

EDUCATION IN BLADDER TRAINING

Evacuation in bladder training can be a tedious and time-consuming method of treatment, and one which requires the constant care and supervision of the parent or nursing staff. It is important that the child be made to perform the "act of micturition" at regular intervals often assisted in the early stages by manual expression of the bladder. The time interval between the acts of micturition has to be carefully calculated, and if rigorously observed will keep the child relatively dry by day. This method of treatment, however, is only of value in those children with minimal incontinence associated with some degree of retention with residual urine. Success can be obtained in this type of case only by meticulous attention to detail, and achieves but a relatively normal existence.

EXPRESSION OF THE BLADDER

Expression of the bladder has proved to be of great value in patients who have an ineffective detrusor mechanism and who are unable, in their attempts to empty the bladder, to overcome the resistance of the bladder neck and external sphincter. Expression of the bladder may be performed either by contraction of the abdominal musculature or manually, and it has been shown that whenever possible it is better to utilize the former method. Manual expression of the bladder always has the attendant risk of ureteral reflux, which is rarely seen when contraction of the abdominal musculature is used. It is not possible, however, to carry out this ideal method in many of these patients, owing to poor development of the abdominal musculature or alteration of the body contour due to other skeletal defects. In this type of case manual expression of the bladder performed by exerting a downward and backward pressure on the bladder, in the region of the hypogastrium, is the only method which can be utilized. The co-operative patient may be trained to do this personally, but often some extra assistance or supervision is needed.

When the resistance of the bladder neck or external sphincter is high, this method is not entirely without risk as ureteral reflux can occur quite easily, which in turn can produce degenerative changes in the upper urinary tract. The success of bladder expression can be judged only by repeated estimation of the residual urine which should be checked at regular intervals. A most valuable combination of methods of treatment is that of re-education in bladder training with expression of the bladder. This is well illustrated in the case of a young girl who sustained an injury to the cauda equina from a fragment of glass. She subsequently developed urinary incontinence due to retention with overflow, with a large amount of residual urine. Meticulous time training and bladder expression was instituted, and she has remained in good health with adequate bladder control and has returned almost to normality.

APPARATUSES TO CONTROL INCONTINENCE

From very early times various ingenious appliances have been devised to control urinary incontinence. However, for anatomical reasons, these are only of value in the male. Recent development in lightweight plastics has enabled appliances which were formerly cumbersome and heavy to be manufactured of much lighter

treatment of urinary incontinence of neurogenic origin especially in cases of spina bifida. Similar operations have been devised in an attempt to cure the incontinence by a resection and suture of the anterior portion of the prostatic capsule. Cases have been recorded in which these methods of treatment have resulted in increased obstruction at the bladder neck with ureteric reflux and back pressure effects on the upper urinary tract.

Permanent suprapubic fistula

Various ingenious operations have been devised to close the bladder neck completely with establishment of a permanent suprapubic fistula. Many surgeons hold that a controlled suprapubic fistula is far superior to an incontinent vesical neck and urethra. This operation is of particular value in the female child, in whom the urethra is completely transected below the bladder neck, the bladder neck sutured and a permanent suprapubic fistula then established. Gross has popularized this method of treatment and has reported success in many cases (Gross, Holcombe and Swan, 1953).

Modifications of this type of operation, such as urethral transposition, have recently been used in treatment of neurogenic incontinence with success. Lapides, as a result of his experimental studies in dogs, has advocated transection of the urethra and closure of the bladder neck with establishment of a fistula in the suprapubic area. He fashioned an external vesical conduit from flaps of bladder muscle and has shown that after this operation patients can remain continent and expel urine at regular intervals from the stoma by vesical and abdominal contraction. The results in successful cases have been encouraging, and it is recognized that this is a valuable method of treatment and one which can be utilized in patients for whom the establishment of an ileal ureterostomy has not been possible on account of technical difficulties and poor general condition. It is a simpler operation and a safe one even in poor-risk cases.

Ileocystostomy

Cordonnier (1957) described his own technique of ileocystostomy for the treatment of incontinence of micturition of neurogenic cause. In this technique, the urethra is transected and the vesical neck closed; an ileal segment is then fashioned which is subsequently anastomosed to the bladder with its other end opening as an external stoma on the anterior abdominal wall. If the bladder is grossly distended and atonic, resection of the redundant bladder wall is first performed and the ileum then anastomosed to it. The external stoma of the conduit can be efficiently controlled by a well-fitting ileostomy bag: this operation has proved very satisfactory; however, in the present author's opinion, it is difficult to see its advantage over an ileal ureterostomy. It would appear to be a longer and more difficult procedure and one which can present technical difficulties in vesico-ileal anastomosis, especially when there is disproportion between the musculature of the vesical wall and that of the ileum. It has been advocated and acclaimed as a safer procedure as it does not require bilateral ureteric transplantation into the ileal conduit. However, transplantation of the ureters into the ileal loop can be carried out simply and effectively without adding

been impressed with their value; in fact, a proportion have condemned them and refused to agree that they have a place in the treatment of urinary incontinence. Many different techniques have been devised and used, perhaps the most practised group being those which employ the technique of plication of the urethra or the bladder neck. These are of value only in the male child, and the perineal operations of Lowsley and of Millin have been credited with great success, in many cases with complete return of continence.

Plication of the urethra

The principle of the operation is that plication and suture of the bulbospongiosus muscle reduces the calibre of the urethra and increases the urethral resistance. It is an accepted anatomical finding that in young boys the musculature of the bulb and perineum is often exceedingly poorly developed and in certain cases deficient, which makes this operation not only more difficult, but often impracticable. It has proved of value in patients in whom there is a minimal degree of urinary incontinence, but in whom there is some measure of urinary control. Thus it is a valuable adjunct in treatment and has enabled many of these sufferers to obtain employment and again become members of society. The operation must be done with meticulous care to prevent such a severe reduction in the calibre of the urethra as would cause partial retention of urine and associated back pressure effects in the upper urinary tract.

Y-V plasty

Operations on the bladder neck have also become popular and it is interesting to note that the retropubic approach to the bladder neck has, of recent years, been used with increasing frequency in young children in preference to transurethral operations. It is, however, an operation not without technical difficulties, but if carefully performed does give good exposure of the bladder neck, and thereby a more adequate and complete resection. Young and Niebel (1958) advocated their well-established Y-V plasty on the neck of the bladder, after resection of an adequate amount of tissue from that area. He pointed out that this method was far superior to, and gave better results than, the original operation in which the bladder neck was incised longitudinally and sutured in a transverse plane. Complications can naturally follow this operation, the most important being urethro-vaginal and vesico-vaginal fistulae. Paradoxically, cases have been reported of complete incontinence following what appears to be a successful operation; the cause is traction on the external sphincter, and has only occurred in those cases in which there has been a long vertical limb of the Y which has extended almost to the apex of the prostatic urethra. Subsequent healing and fibrosis of the incision has produced traction on the external sphincter resulting in complete urinary incontinence. It is important not to prolong the incision too far into the prostatic urethra.

Sling operation

The sling operation of Millin (1939), though an excellent one for the treatment of incontinence in non-neurogenic cases, has not met with success as a method of

Results

This operation itself produces dramatic and considerable reduction in the volume of residual urine which is due to decrease of sphincteric spasm, whereby a more powerful voiding can be produced.

Nash (1956) reported the benefits of this operation in an adolescent boy who had a high thoracic cord lesion. On account of repeated flexion spasms and troublesome priapism the use of a portable urinal was prevented. Unilateral pudendal neurectomy produced a gratifying relief of the priapism, enabling him to control the urinary incontinence with a portable urinal, and to pursue a course of vocational training. Frequently, this operation has to be combined with a transurethral resection of the bladder neck in order to relieve the distressing urinary symptoms. The present author feels that Band has produced conclusive evidence by his results, that this is an operation worthy of trial, and one which can give great success in the male child.

CUTANEOUS URETEROSTOMY

Formerly, cutaneous ureterostomy was popular with surgeons who devised ingenious operations to fashion nipple-like tube pedicles of skin to drain the ureters and to allow the wearing of an appliance. The long-term follow-up of these cases has not been satisfactory, often the tube pedicles did not function as had been planned, and stenosis of the orifice at the junction of the skin and ureter being some of the more troublesome complications. Also the end result was rather cumbersome as it required the wearing of two appliances to collect urine. Frequently, as a result of the improved general condition and increase in weight of the patient, there was an inevitable alteration in the contour of the abdominal wall and at the same time in the shape of the tube pedicles. These often became "absorbed", the ureterostomy was once more flush with the surface of the abdominal wall, and became a difficult stoma to control. The author feels certain, however, that there is a place, as a temporary measure, for cutaneous ureterostomy in the poor-risk case with grossly impaired function of the upper urinary tract. It enables the patient to be made more fit, associated complications to be corrected and a more extensive and definitive type of operation such as ileocutaneous ureterostomy to be performed at a later date. As a result of improvement in the condition of the patient it is a relatively easy matter to convert a *bilateral cutaneous ureterostomy into an ileocutaneous ureterostomy provided* the stomas of the cutaneous ureterostomy have been well planned and judiciously placed.

URETERO-COLIC ANASTOMOSIS

Uretero-colic anastomosis can only rarely be used in cases of spina bifida on account of the associated impairment, or complete absence, of rectal control. However, it should be noted and mentioned, as a method of treatment, because in two of the cases in this personal series of sacral agenesis good rectal control was present, though there was complete urinary incontinence. It is, as can be appreciated, not without some risk if there is gross dilatation and impairment

to the operative risk, and it is therefore difficult to see the validity of these statements.

PUDENDAL NEURECTOMY

In a proportion of the cases with neurogenic dysfunction of the bladder, it has long been appreciated that there is an increase in the tone or spasm of the external sphincter, which has prevented an efficient, and complete emptying of the bladder. Band (1945), Ross and Damanski (1953) have reported considerable success and improvement in the urinary symptoms in paraplegics following this operation. Pudendal neurectomy was first practised by Rochet (1889) to relieve retention, which he thought was due to spasm of the striated muscle of the posterior urethra. Bors and his colleagues (Bors and Commar, 1952; Bors, Commar and Rheingold, 1954) have conclusively shown that there is a definite proportion of striated muscle fibres in the region of the posterior urethra and the bladder neck. They also showed that stimulation of the medial branch of the pudendal nerve would cause contraction of these muscle fibres, and of the posterior urethra and the bladder neck. It was therefore postulated that improvement in voiding would be produced by division of the pudendal nerve.

Technique

The patient is placed flat on his face and the operating table angled at the pelvis so that the hips can be flexed almost to a right angle (Fig. 114). Before making the incision, it is advantageous to retract the skin laterally over the ischial tuberosity, so that the operation scar then lies medial to the tuberosity and is not in a position which might lead to subsequent pressure sore. The incision is deepened so that the operator can expose the outer wall of the ischio-rectal fossa. The neurovascular bundle is found in the normal position in Alcock's canal, and the inferior haemorrhoidal nerve is then exposed, as it is a valuable guide to the main nerve trunk. It is essential to trace the pudendal nerve almost to the edge of the sacrum and there to divide it, resecting a short length of nerve tissue. It is important to be certain that the entire nerve is resected. The nerve varies in composition, Bors and Commar (1954) found that in a series of 50 cases a solitary nerve trunk was present in 16, two nerve trunks in 23, and in all cases there were three divisions of the pudendal nerve.



FIG. 114.—Pudendal neurectomy. Drawing of position of patient on table and incision used.

Technique

The operation of ileal ureterostomy is now so well known that only a brief account is given of the operative technique. It is important that the solitary external stoma should be sited at a convenient place on the anterior abdominal wall which permits the wearing of a watertight drainage apparatus and one which is readily controlled by the patient. One case in the series is a small girl aged 5 years, who is now attending school regularly having learned to manage the ileostomy bag effectively herself. Personal experience of the operation has shown that it is advantageous whenever possible to intubate the ureters with a polythene tube of small calibre, and to bring these tubes out through the external stoma thus allowing free drainage from the ureters during the immediate post-operative period. Often mucoid secretion from the ileum can interfere with drainage from the external stoma, but with intubation this obstructive factor is alleviated. Experience has also shown that it is important not to have a longer loop of ileum than is necessary because the loop increases both in circumference and length after operation. It is also important to see that it is snugly anchored to the peritoneum of the postero-lateral abdominal wall. The loop should act purely as a conduit for urine and not as a reservoir, and therefore in this respect it is imperative to use only the requisite amount of ileum. The basic steps of the operation are as follows.

The patient is prepared for operation by giving a low residue diet with adequate dosage of aureomycin four hourly for two days before operation. The distal colon is washed out on the morning and evening before operation. It is preferable to open the abdomen by a left paramedian incision of adequate length to afford good exposure, and a general inspection of the abdomen is then made. After careful scrutiny of the terminal ileum, a suitable portion of bowel is selected in the lowest three feet and about twelve inches in length after giving due consideration to its vascular supply. It is inadvisable to transect the ileum less than eight inches from the ileo-caecal junction. It is also important to select a portion of ileum the mesentery of which is sufficiently long and mobile to enable it to lie in the right iliac fossa. One end of the isolated loop is passed through a stab incision in the abdomen to form an external stoma; there must be no tension or impairment of the blood supply of this ileal segment. The selection of the loop must be made with meticulous care and it is undoubtedly the most important factor in the success of the operation. Continuity of the intestinal tract is then restored in front of the isolated loop (Fig. 115).

In small children it is tempting to use a lateral rather than an end-to-end anastomosis because a larger stoma can be made and there would therefore appear to be less risk of oedema in the post-operative period. Often following the operation there is troublesome ileus, and it might be expected that this would be obviated by the larger stoma. Nevertheless there is experimental and clinical evidence that the late result of a lateral anastomosis, especially one with a large stoma, is unsatisfactory because of interference with intestinal peristalsis. An end-to-end union is therefore preferred.

The ureters are exposed and mobilized through a vertical incision in the posterior parietal peritoneum at the brim of the pelvis; they are divided as low as possible

of function of the upper urinary tract. The inevitable hyperchloraemic acidosis which occurs in this type of case can cause considerable trouble. In one of the cases of the sacral agenesis series, that of a young girl with good rectal control, uretero-colic anastomosis was performed at the age of four years. She has developed normally with a normal adolescence and is now aged 15 years. Of recent years, however, there has been increasing evidence of deterioration of function in the upper urinary tract with more frequent episodes of hyperchloraemic acidosis. It is probable that ileocutaneous ureterostomy may have to be performed in the near future to conserve renal function and prevent further renal damage.

Another case in the series, that of an adult male with complete sacral agenesis, had uretero-colic anastomosis performed eight years ago with a satisfactory initial result and subsequent good health for a period of six years. He is now showing early signs of increasing upper urinary tract damage, with recurrent but mild attacks of urinary infection. These complications have necessitated a critical review of the future conduct of treatment, and it is probable that he will have to be submitted to an ileocutaneous ureterostomy. A further case in a young boy presented additional complications in that rectal control was so grossly impaired that it caused nursing problems and interfered with any form of rehabilitation. A left iliac colostomy was established, and the lower portion of the rectum was then closed; the ureters were transplanted into the distal portion of the rectum thereby forming a recto-sigmoid bladder with an external stoma. In spite of the fact that two stomas were constructed, the child has remained fit and well and with increased comfort, the general management and rehabilitation being more easy than before the operation was performed. Such a case is rarely encountered, but when it is, the problem of management is formidable.

ILEAL URETEROSTOMY

The operation of ileal ureterostomy (ileal bladder) has undoubtedly revolutionized the treatment of urinary incontinence of neurogenic origin. It has been established as a safe and practical procedure, and should be used in the female whenever the degree of urinary incontinence prevents or embarrasses education, vocational training and employment. In the male, it is employed when incontinence is severe and cannot be quickly and easily controlled by more simple methods.

It is imperative to have a carefully planned programme, and not to use this method as a last resort when many others have failed. Valuable time is lost, with marked deterioration of renal function due to procrastination and the practice of ineffectual operations. Improvement in the physical condition and the general attainments of these children, and above all in the morale, is often quite astounding, and three children in this series were able, with the aid of ileal ureterostomy, to attend school and mix freely with others of their own age. Pyrah and his colleagues (1955) have shown that this operation is safe and is particularly free of biochemical complications. However, in cases with severe renal impairment recurrent mild attacks of upper urinary tract infection have still occurred after operation, but have always responded readily to treatment without the complication of hyperchloraemic acidosis.

and relieved from the distressing urinary incontinence, and is socially acceptable and able to return to work. Hyperchloraemic acidosis is rare and the radiological tests of renal function are very satisfactory.

Choice of operation

Ileal ureterostomy has been so successful and produced such good clinical and functional results that it is now the operation of choice which the author employs in all cases when urinary incontinence is at all marked. In girls in whom the incontinence cannot be controlled by the more simple methods of bladder training and manual expression of the bladder, it is a justifiable procedure and definitely indicated. In boys with complete incontinence without residual urine, in whom other operative measures have failed, or in those cases where the wearing of an appliance presents a problem to rehabilitation, it is desirable to use this method.

However, when residual urine is accompanied by clinical evidence of increased sphincteric tone or obstruction at the bladder neck, a combination of manual expression and transurethral resection of the bladder neck should be employed in the first instance. If, however, no improvement occurs after a short period of specially supervised training in hospital, and in the absence of any other contra-indication, ileal ureterostomy should be immediately performed.

In patients with retention of urine and overflow with back pressure phenomena, the author considers that ileal ureterostomy should be performed as an initial procedure, as there is very little hope of improvement in urinary control or of preserving renal function by performing transurethral resection of the bladder neck.

BIBLIOGRAPHY AND REFERENCES

Band, D. (1945). *Brit J. Urol.*, **17**, 1.
Bors, E. (1952). *J. Urol.*, **67**, 6.
— and Commar, A. E. (1952). *J. Urol.*, **68**, 691.
— — and Rheingold, I. M. (1954). *Ibid.*, **72**, 191.
Cordonnier, J. J. (1957). *J. Urol.*, **78**, 505.
Emmett, J. L., and Dunn, J. D. (1946). *Surg. Gynec. Obstet.*, **83**, 597.
— Daut, R. V., and Dunn, J. D. (1948). *J. Urol.*, **59**, 430.
Freedman, B. (1950). *Brit. J. Surg.*, **37**, 299.
Gross, R. E., Holcombe, G. W. Jnr., and Swan, H. (1953). *Arch. Surg.*, **66**, 143.
Leadbetter, W. R. (1951). *J. Urol.*, **65**, 818.
Millin, T. (1939). *Proc. R. Soc. Med.*, **32**, 777.
Nash, D. F. Ellison (1956). *Brit. med. J.*, **2**, 1333.
— (1956). *Ann. R. Coll. Surg. Engl.*, **20**, 349
Nesbit, R. (1948). *Univ. Hosp. Bull. Mich.*, **14**, 45.
Pouset, F. (1938). *Lyon. chir.*, **35**, 371.
Pyrah, L. N. (1956). *Brit. med J.*, **1**, 335.
— (1956). *Brit. J. Urol.*, **28**, 363.
— (1956). In *British Surgical Practice, Surgical Progress, 1956*, p. 162. London: Butterworth.

and the distal cut ends are ligated. The uretero-ileal anastomosis can be made by any of the standard techniques depending on the personal preference of the surgeon. Irrespective of the technique employed the ureters should be implanted into the antimesenteric border of the loop approximately 4 and 10 centimetres from the proximal end. If there is any dilatation of the ureter a technique such as that of Cordonnier, Nesbit or Leadbetter, which utilizes the direct mucosal anastomosis, is preferable. By rotating the loop at the time of anastomosis it is possible to get a very accurate uretero-ileal anastomosis. The external stoma should be sited on the abdominal wall at a previously determined place and it is important to fashion a spout of ileum by everting the mucous layer over the muscle coat and suturing it to the skin. The main incision is then closed by any of the

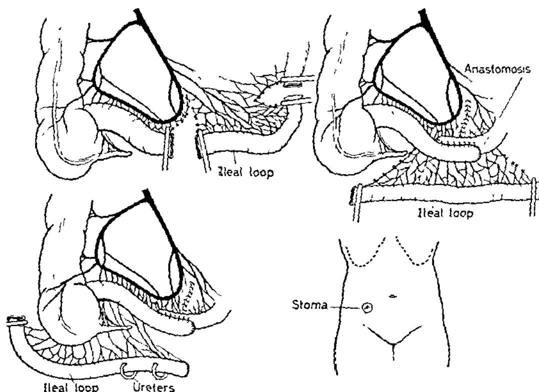


FIG. 115.—Ileocutaneous ureterostomy. Schematic drawing to illustrate method and steps of operation in which a lateral anastomosis has been used; however, see text for discussion.

standard techniques. As already mentioned, the author's preference is to intubate the ureters at the time of anastomosis with polythene tubes which are then brought out through the external stoma to drain into individual receptacles. When the danger of post-operative ileus has passed and secretion from both ureters is satisfactory, the polythene tubes are removed and a Rutzen bag employed as the collecting apparatus for urine from the ileostomy. The use of modern adhesive cements will allow a watertight fit. The late results of this operation are very satisfactory, the patient appears in good health, and looks well, is comfortable

was closed. Strips of the excised mucosa were transplanted to the denuded ileal segment and held by sutures. The segment was shaped into a tube and sutured round a polythene splint. The ureter was excised between the uretero-pelvic and uretero-vesical junctions; then one end of the ileal segment was anastomosed to the proximal cut end of the ureter, with the splint inserted into the renal pelvis. After implantation of the distal end of the segment into the posterior wall of the bladder the splint was removed, the posterior peritoneal edges were approximated and the abdominal wound was closed. Healing occurred in all cases. Subsequent examination of the ileal segments revealed smooth surfaces with good fixation of the submucosa or muscularis lining to the vesical mucosal patch grafts. Cystograms showed no evidence of reflux. In some cases hydronephrosis was a temporary complication 2–5 weeks after the operation. The authors conclude that the operation satisfies the criteria of active peristalsis, absence of reflux, electrolyte absorption or mucous secretion, and freedom from urinary stasis or infection.

Ileal bladder

Physiological response

JUDE, HARRIS and SMITH (1959) reported on the use of the ileal bladder in the management of 14 cases of advanced carcinoma of the cervix uteri and 7 cases of carcinoma of the urinary bladder. In the latter group high-voltage irradiation was also employed. The series included a case in which the ileal-bladder technique was adopted as a temporary measure in the management of a large uretero-vesicovaginal fistula. With reference to details of the surgical procedure the length of the ileal segment was 20–25 centimetres and the uretero-ileal anastomosis was effected by means of the two layer mucosa-to-mucosa end-to-side technique. The opening of the ileostomy was constructed in the right lower quadrant of the abdomen and the urine was collected in a disposable plastic bag. The patients remained under observation for periods ranging from six months to more than two years after the operation. Serial examinations included intravenous and retrograde pyelograms, renal function studies and tests for serum electrolytes. The investigators found that renal function had been maintained. There were no major changes in the serum-electrolyte levels, but minor changes in the levels were detected in several patients with a history of chronic pyelonephritis. The ileal segment provided a protective mechanism against retrograde infection of the kidneys, and normal renal function was thereby preserved. An episode of acute infection was recorded in a patient with temporary obstruction of the ileostomy stoma. In this case, however, there was a good response to routine treatment.

Rectal bladder

WILKINS and WILLS (1959) described the technique of constructing a rectal bladder. The authors are of the opinion that the operation constitutes the simplest means of counteracting uraemia and hyperchloraemic acidosis after uretero-intestinal anastomosis. After removal of the diseased tissue, including the urinary bladder, a mucosa-to-mucosa technique is employed for implanting the ureters into the lateral wall of the rectum or rectosigmoid. The bowel is divided and closed immediately above the site of implantation. It is advisable to bring the proximal end of the bowel through the left lower quadrant to form a dry colostomy. In order to prevent distension or back pressure catheter drainage of the rectal bladder is employed for 10–14 days. Sulphonamides and antibiotics are administered during the post-operative period. Most patients are able to control the urine during waking hours, but slight leakage may occur at night. Leakage is controlled by the administration of antispasmodic drugs and by limiting the intake of fluid during the evening. Catheter drainage of the rectum increases the danger of infection. Wilkins and Wills report on the case of a man, aged 67 years, with carcinoma of the bladder. As uraemia developed after cystectomy and uretero-intestinal anastomosis a rectal bladder was constructed and good palliation was achieved. Satisfactory results

Pyrah, L. N., (1957). *J. Urol.*, **78**, 683.
— and Raper, F. P. (1955). *Brit. J. Surg.*, **42**, 337.
— Care, A. D., Reed, G. W., and Parsons, F. M. (1955). *Ibid.*, **42**, 357.
Rochet, V. (1889). *Arch. prov. Chir., Paris*, **312**, 321.
Ross, J. C., and Damanski, M. (1953). *Brit. J. Urol.*, **25**, 45.
Stephens, F. D. (1953). *Aust., N.Z. J. Surg.*, **22**, 161.
Williams, D. I., and Nixon, H. H. (1957). *Surg. Gynec. Obstet.*, **105**, 84.
Young, B. W., and Niebel, J. D. (1958). *J. Urol.*, **79**, 838.

SELECTED ABSTRACTS

Congenital deficiency of abdominal musculature

Obstructive uropathy

Discussing congenital deficiency of the abdominal musculature, McGovern and Marshall (1959) stated that the condition rarely affects females. The syndrome is attributed to general embryological deficiency rather than to a localized defect of the abdominal wall, urinary tract or nervous system. Sometimes the deficiency is limited to one quadrant of the abdomen. In severe cases, however, the whole anterior abdominal wall and part of the posterior wall may be affected. If muscular inadequacy impairs respiration pulmonary infection may ensue. The abdominal skin tends to be wrinkled and movements of the intestines are outlined through the flabby wall. Bilateral cryptorchidism is a common finding. Abnormalities may include pigeon breast, Harrison's groove and deformities of the gastro-intestinal tract. Anomalies of the cardiovascular system and deformities of the lower extremities may be present. Obstruction of the urinary tract may cause death due to renal deficiency or urinary sepsis. Examination may reveal the presence of hydronephrosis, a large thicked-walled bladder, a patent urachus and obstruction of the uretero-vesical junction. With reference to the management of the condition, when cystography and intravenous pyelography fail to yield the required information, exploratory cystostomy with ureteral catheterization and retrograde pyelography should be performed. If the abnormality is sufficiently severe to warrant surgical intervention treatment consists in preliminary bilateral nephrostomy. Excessive lengths of the ureters are excised and then the ureters are re-implanted into the base of the bladder. Open surgical plastic revision of the vesical outlet is preferred to transurethral resection. Re-evaluation techniques include pyelo-ureterograms through nephrostomy catheters and determination of drainage pressures by means of a burette attached to the nephrostomy. In the series described by the authors three of seven patients died during early infancy. One patient, aged 15 years, showed a diffuse muscle defect of the right side of the abdomen.

Ureteral substitute

Uroepithelial lined small bowel

Martin, Duxbury and Leadbetter (1959) described experiments in which an intact intestinal segment was employed as a ureteral substitute. In a series of abdominal operations on dogs the terminal ileum was exposed through a midline incision. A segment of the ileum was isolated between clamps and care was taken to maintain the blood supply. Intestinal continuity was restored by end-to-end anastomosis and the isolated ileal loop was opened along the antimesenteric border. The ileal segment was denuded either of mucosa or of both mucosa and submucosa. After removal of the Peyer's patches the segment was narrowed longitudinally. In the next phase of the operation the urinary bladder was exposed and partially distended with sterile saline solution. The anterior wall of the bladder was incised and a portion of the mucosa was removed. A small mushroom catheter was inserted through a separate stab wound and the bladder

VIRUSES AND SURGICAL DISORDERS INCLUDING CANCER

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INTRODUCTION

Apart from chapters on rabies and zoster virus and mention of the possible viral aetiology of Bell's palsy and of sterile effusions, little attention has been paid to virus diseases in previous volumes of *Surgical Progress*. The reason for this is quite simply that so far as is known, virus infections rarely require surgical attention. On the other hand the fact that virus infections may have to be considered in the differential diagnosis of some surgical disorders and the possible viral aetiology of certain tumours make viruses worthy of some consideration by surgeons. In this chapter a brief description of the property of viruses and the diagnosis of virus infections is followed by a discussion of the virus infections which a surgeon might encounter, and a short survey of work on the virus aetiology of tumours.

PROPERTIES OF VIRUSES

Viruses are infectious entities which can multiply only inside living cells. The larger viruses such as the pox viruses and viruses of the psittacosis-lymphogranuloma venereum group which measure about 250 millimicrons can be seen with an ordinary microscope but all other viruses are submicroscopic and measure from 20 to 130 millimicrons in diameter. The fact that viruses are submicroscopic obligate parasites of living cells means that they cannot be studied with the same techniques as are used in bacteriology. Viruses will not grow in broth cultures or other bacteriological media and are usually studied by their effect on tissue cultures, embryonated eggs or animals. Tissue culture techniques involve the growth of living cells in test tubes. These are inoculated with virus suspensions and the effect which the viruses have on the cells is observed under the ordinary microscope.

were also obtained in five cases of carcinoma of the cervix uteri. One patient survived for 22 months without symptoms referable to the genito-urinary tract. Another patient remained active for 18 months and eventually succumbed either to carcinoma or to progressive renal damage. No significant electrolyte imbalance was recorded and there was no evidence that pyelonephritis had developed as a result of the rectal bladder operation.

REFERENCES

Jude, J. R., Harris, A. H., and Smith, R.R. (1959). *Surg. Gynec. Obstet.*, **109**, 173.
Martin, L. S. J., Duxbury, J. H., and Leadbetter, W. F. (1959). *Surg. Gynec. Obstet.*, **108**, 439.
McGovern, J. H., and Marshall, V. F. (1959). *Surg. Gynec. Obstet.*, **108**, 289.
Wilkins, S. A. Jnr., and Wills, S. A. (1959). *Surg. Gynec. Obstet.*, **109**, 1.

what specimens are needed. Virus techniques are developing rapidly: the laboratory diagnosis of a disease may be impossible this year but possible next year, and the specimens required may vary as techniques improve.

SOME VIRUS DISEASES OF IMPORTANCE TO SURGEONS

Mumps

About half of all infections with mumps virus are asymptomatic. In clinical infections the salivary glands, particularly the parotids, are commonly affected, but practically any organ in the body may be involved. After parotitis the most common results of infection with mumps virus are aseptic meningitis, orchitis, oophoritis and pancreatitis. Other conditions such as encephalitis, neuritis of the facial and trigeminal nerves or inflammation of the epididymis, prostate, liver and thyroid may also occur.

Parotitis is usually bilateral, although one side may be involved first, to be followed a few days later by swelling of the other gland. The other organs can be affected before or after the parotitis or at the same time, and also when there are no signs of inflammation of the salivary glands. Orchitis occurs in about 20 per cent of mumps infections after the age of puberty, but rarely leads to sterility, perhaps because it is seldom bilateral.

Diagnosis

The clinical diagnosis of mumps parotitis should present no problem during epidemics but the diagnosis of sporadic cases may be difficult particularly when parotitis is unilateral. The differential diagnosis includes such conditions as suppurative parotitis, foreign bodies in the salivary duct, neoplasm and Mikulicz's disease and other rare conditions. When involvement of other organs occurs in association with salivary gland swelling there is again no difficulty in diagnosis. On the other hand, when salivary gland swelling is minimal or absent, it is practically impossible to make a diagnosis on the clinical findings alone and the provisional diagnosis will usually have to be confirmed by epidemiological observation or by serological laboratory tests. As with most serological tests a definite diagnosis can usually be made only if two specimens of serum are available, but in the case of mumps an early presumptive diagnosis can sometimes be made on a single serum taken soon after the onset of illness.

Treatment

There is no specific treatment and antibiotics or chemotherapeutic drugs are of no value. Various attempts have been made to prevent the onset of orchitis in young adults by giving large intramuscular injections of *gamma*-globulin or concentrated pooled convalescent serum. This has not been adequately investigated, but is probably worth trying. No effect can be expected by giving *gamma*-globulin after symptoms of orchitis have developed. There is no indication that steroid hormones are effective in the treatment of orchitis during the acute phase of the illness and in our opinion their use is contra-indicated. In severe orchitis it may be necessary to relieve the testicular pressure—caused by oedema—by incision of the tunica albuginea.

The multiplication of viruses in tissue culture cells is nearly always associated with destruction of the cells and liberation of virus particles capable of infecting other cells. The destructive effect of the virus is called the cytopathic effect (CPE) and the quantity of virus present in a specimen can be measured by finding the highest dilution of the material under test which will produce a CPE. The CPE can be prevented by mixing the virus with specific immune serum and this is the basis of neutralization tests for identifying an unknown virus or demonstrating antibody in serum against a known virus. Other viruses such as influenza and mumps virus grow best in embryonated eggs. These viruses can multiply in the cells of the allantoic or amniotic cavity without producing recognizable lesions, and virus is released in large amounts into the amniotic and allantoic fluids and can be demonstrated by its ability to agglutinate red cells. Again the quantity of the virus can be estimated by finding the highest dilution of fluid which will haemagglutinate, and haemagglutinating viruses can be identified by specific immune serum which inhibits haemagglutination.

Animals are used much less nowadays than they used to be for virus studies, but they are still employed for the isolation of certain viruses (for example some of the Coxsackie viruses, *see* page 373) which so far can only be grown in certain animals. They are also used in virulence tests. Titrations of virus and neutralization tests can be performed in animals in the same manner as in tissue culture.

DIAGNOSIS OF VIRUS INFECTIONS

While virus isolation is the most rapid and optimal method of diagnosis of some virus infections such as poliomyelitis, herpes and smallpox, it is not normally attempted in mumps, influenza or in many other diseases. The reasons for this are that specimens from patients suffering from infections with these viruses are often taken after the period of infectiousness, and the specimen will contain no virus, and that the isolation of a virus and its identification may take a long time. In consequence serological tests are often a more convenient diagnostic procedure. For the serological diagnosis of a clinical or subclinical infection, two samples of clotted blood are required which are usually referred to as paired sera. The first sample should be taken during the acute phase of illness and the second sample two or three weeks later. The two sera are then tested to find out if antibody has developed or if there has been a significant rise of antibody in the convalescent serum sample. It will be obvious that if just a convalescent serum sample is taken from a patient and it is found to have antibody, all that one can conclude is that some time in the past the patient has had an infection with the particular virus in question. It must be appreciated that with a few exceptions, such as poliomyelitis and the pox diseases, virological techniques have not been able to provide the rapid answers which the clinician expects from most bacteriological specimens at the present time, and only in a few infections can viral diagnosis be rapid enough to influence treatment in the early stages of infection.

Because of the time which the diagnosis of many virus diseases takes routine laboratory tests are not used extensively. However, surgeons wishing to make use of such diagnostic procedures as are available would be well advised to telephone the laboratory and inquire whether it can be of any help, and if it can

susceptible person, whereas zoster represents invasion by nerve pathways in people with some resistance and circulating antibody.

Zoster is characterized by inflammation of dorsal root ganglia or of the extramedullary ganglia of cranial nerves, and is accompanied by crops of vesicles which resemble those of varicella, except that typically they involve one or more dermatomes producing a bandlike distribution of lesions. The most common symptom is pain which may be dull, stabbing, sharp or burning and this often precedes the appearance of skin lesions by as long as ten days. The pain may be very severe and if the lumbar ganglia are affected may simulate appendicitis, cholecystitis, pleurisy or perinephric abscess. Post-zoster neuritis may continue for months or years after the skin is healed. Wyburn-Mason (1957) has drawn attention to visceral lesions which may accompany zoster, such as involvement of the urinary bladder and various gastro-intestinal symptoms including ileus. In areas supplied by the cranial nerves the most common site of zoster is the ophthalmic division of the trigeminal nerve but the geniculate, auditory and vestibular, glossopharyngeal and vagus ganglia may be involved. In addition to pain and vesicles, there may be a wide variety of symptoms such as headache, reduced vision, weakness of the levator palpebrae, Bell's palsy, paralysis of the larnyx or pharynx and cardiac or gastric distress. It should be remembered that zoster without skin lesions may occur.

Zoster is a recognized complication following surgical procedures on the gasserian ganglion for trigeminal neuralgia (*see* herpes simplex below). It has also followed various other traumas or stimuli such as tumours, tuberculosis, leukaemia and so forth. This is of clinical importance for in certain individuals the possibility of cancer or leukaemia should be considered in a patient with zoster. The diagnosis does not usually require assistance from the laboratory except to rule out other viruses, such as herpes simplex, vaccinia or smallpox, which can cause vesicular lesions.

Treatment

Antibiotics may be useful in reducing secondary bacterial infection in debilitated elderly patients but "their use seems unjustifiable in the routine treatment of zoster" (Carter, 1951). The use of cortisone is contra-indicated and there is no evidence that roentgen ray treatment is of any value. Local symptomatic treatment of the skin with calamine lotion, or with an antipruritic ointment is of help in relieving irritation and discomfort.

Herpes simplex

Herpes simplex is one of the most widespread viral infections of man. The virus may produce stomatitis in children and then lie dormant to be reactivated in later years by various excitants, such as temperature changes and trauma, and give rise to vesicular eruptions on the skin particularly at mucocutaneous junctions. It is of interest to surgeons because of its possible association with trigeminal neuralgia (Knight, 1957), and as the aetiological agent in a certain type of whitlow (Stern and his colleagues, 1959).

Mention has already been made of the association between zoster and trauma to the gasserian ganglion. Knight suggested that herpes simplex may be an

Lymphogranuloma venereum (LGV)

Infection with LGV virus is nearly always by sexual contact but extragenital lesions may occur and surgeons have developed hand infections when removing infected glands. The primary lesion which is herpetic or nodular in appearance breaks down into a shallow ulcer with clean cut edges. The infection may terminate at this stage or else the virus may spread by lymphatic vessels to the regional lymph nodes with consequent unilateral or bilateral adenitis of the inguinal, intrapelvic or deep pelvic and perianal nodes. The infection may resolve at this stage but in about 50 per cent of infections the regional nodes suppurate. This gives rise to constitutional symptoms and sometimes a generalized lymphadenopathy occurs. The tertiary stage may present a wide variety of lesions, the clinical details of which are described fully by Favre and Hellerstrom (1954). In general there may be granulomatous involvement of the vulva, elephantiasis of the external genitalia (esthiomène), proctitis and rectal stricture with fistula formation. The histological changes in the lymph nodes and adjacent granulomatous tissue are characterized by dense infiltration with mononuclear cells, especially plasma cells, and nodular accumulations of epithelioid cells and giant cells followed by necrosis leading to widespread tissue destruction.

Diagnosis

Lymphogranuloma venereum presents a problem to the surgeon in the differential diagnosis of adenitis of the glands draining the genital region, carcinoma and tuberculosis of the rectum and the venereal diseases. The diagnosis can usually be established by isolation of the virus, by serological tests, or by the Frei test in which an intradermal injection of 0·1 millilitre of heated or otherwise inactivated virus is given. The Frei test is read like a tuberculin test; in an infected individual a papule develops at the site of inoculation. The skin reaction usually becomes positive from one to six weeks after infection and probably remains so for life. It is a specific test for infection with a member of the LGV-psittacosis group of viruses and the results of skin tests closely parallel serological tests, but it should be remembered that it is a group reactive test and positive reactions may occur following infection with psittacosis virus.

Treatment

The LGV-psittacosis group of viruses, unlike other viruses, are susceptible to chemotherapy and antibiotics. The results of treatment with sulphonamides have been good particularly in the early stages of the disease. Tetracyclines or intramuscular chloramphenicol may be useful in cases which fail to respond (King, 1959).

Herpes zoster

Herpes zoster (shingles) virus is unrelated to herpes simplex and is probably identical with varicella (chicken-pox). This is concluded from both laboratory and epidemiological evidence, for zoster in adults can result from exposure to cases of chicken-pox, and a patient with zoster can cause chicken-pox in child contacts. It is probable that varicella represents blood spread of the virus in a

tested in this way. It is generally agreed that if the patient's vital capacity is but half to one-third of what is taken as normal then artificial respiration is required (Walley, 1959). In children it is often not possible to test the vital capacity, but Walley noted that experience has shown that if a child has no definite arm weakness, can cry loudly or sleep soundly there is no need for artificial respiration.

If the patient is conscious and the bulbar muscles are unaffected Russell (1958) recommended a tank type of respirator. He pointed out that in bulbar cases with a "death rattle" in which the patient is unconscious early in the illness, apparently complete recovery often occurs if the patients are properly tended in the acute stage. The immediate treatment consists of getting the patient into the prone position, raising the foot of the bed and arranging immediate transfer to a suitable centre (Macrae, 1959). It is recommended that an anaesthetist should accompany the patient while being transferred to hospital with all the necessary equipment to allow swallowing without danger of inhalation. Further treatment consists of the skilled exploitation of postural drainage and intermittent positive pressure respiration.

Coxsackie virus infections

During the past ten years a large number of different viruses has been found in the faeces. These viruses form a group called the enteroviruses and include poliomyelitis, Coxsackie and ECHO viruses. The most common complication of infection with the enteroviruses is probably aseptic meningitis but the group B Coxsackie viruses may also cause myalgia or pleurodynia with or without an associated meningitis and cases may occur sporadically or in epidemics (epidemic myalgia or Bornholm disease).

The onset of symptoms is very abrupt and is associated with severe, often excruciating pain and fever. In adults the pain is usually thoracic but abdominal pain which is frequently periumbilical or on the right side of the abdomen is common in children. The pain may last for 2–14 days and is intensified by movement, and may be associated with tenderness and occasionally swelling of muscle bundles.

Diagnosis

During an epidemic of pleurodynia the diagnosis is usually easy when the pain is thoracic, with or without signs of meningitis. When the pain is abdominal the differential diagnosis should include acute appendicitis, cholecystitis, acute pancreatitis or peptic ulcer, and infection with Coxsackie virus may explain some of the histologically normal appendices removed at operation. In Coxsackie B infection nausea and vomiting are rare, the tenderness which may be present over the site of the pain is superficial: there is seldom any cutaneous hyperaesthesia and the leucocyte count is usually relatively normal.

Encephalitis

Mention has already been made of stupor which may be associated with polioencephalitis. Encephalitis due to other viruses may present a problem in differential diagnosis to the surgeon. The onset in viral encephalitis may be accompanied

aetiological factor in trigeminal neuralgia and that just as recurrences of herpetic lesions of the skin may occur so also may recurrent disturbances of the trigeminal nerve. He stated that in a neurosurgical unit, post-operative herpes simplex occurred in 60 per cent of cases. It is unfortunate that few of his conclusions are based on adequate virological studies but they are of interest in view of recent observations by Stern and his associates on herpetic whitlows in nurses in neurosurgical units. These whitlows consist of coalescing vesicles with small deep vesicles beyond the edge of the lesions. They contain no pus but if the lesion is incised secondary infection occurs. The original infection probably occurs from the respiratory and pharyngeal secretions of patients who are carrying herpes simplex virus.

Treatment

Antibiotics have no specific effect on herpes simplex virus. They may be used to control secondary bacterial infections. The use of cortisone is contra-indicated and the management of skin lesions is symptomatic with calamine lotion, and so forth. The best management of herpetic whitlow is strict non-interference, and prevention by ensuring that nurses who handle suction apparatus wear rubber gloves.

Poliomyelitis

There are three types of poliovirus, types 1, 2 and 3, and type 1 virus is responsible for about 80 per cent of all paralytic infections. It is not proposed to discuss the epidemiology or clinical diagnosis of poliomyelitis except to say that transmission is by person-to-person contact either by faeces or pharyngeal secretions. There is good evidence from North America that three properly spaced injections of inactive virus vaccine (Salk type) have an effectiveness of at least 90 per cent in preventing paralysis in children. It also seems probable that vaccination with inactive vaccine will reduce the spread of virus in the community, but paralytic cases may still occur in inadequately or non-vaccinated individuals.

While paralytic poliomyelitis is essentially a medical disease it is important to remember that poliovirus may cause encephalitis with stupor and this may be confused with other acute cerebral conditions. Stupor may also arise in poliomyelitis from cerebral anoxia. It is important to recognize cases in which life is threatened by respiratory failure before severe anoxia develops so that they may be given experienced medical and nursing care.

Respiratory failure may be due to paralysis of the intercostal muscles and diaphragm or to paralysis (bulbar) of the muscles of swallowing and so on giving rise to obstruction of the airway, or to both. Recognition of respiratory failure is simple when such danger signs as cyanosis, panting respiration, movement of the alae nasi, sternomastoids, and other muscles are present. In the case of bulbar paralysis adults can usually describe their difficulties, but recognition in children may be dependent on observations that the child refuses to eat or drink. Bubbling of secretions makes the diagnosis obvious. The early recognition of respiratory failure is most important and can be diagnosed by estimations of the vital capacity. This can be tested clinically in adults by getting the patient to count out so far as he can after a deep breath and comparing this with one's own vital capacity

diagnosis includes other causes of jaundice, particularly post-hepatic obstructive jaundice, and a final diagnosis may be dependent on needle biopsy or laparotomy.

Treatment and prophylaxis

Treatment is essentially medical and will not be discussed. Prevention of infectious hepatitis depends on accurate reporting of all cases and on good personal and community hygiene.

Because of the possibility of blood spread of infectious hepatitis, all syringes, needles, blood counting pipettes and so forth should be sterilized by autoclaving. *Gamma*-globulin is of value in preventing secondary cases in families and institutions. Prevention of serum hepatitis again depends on complete sterility of needles and instruments of all kinds, the exclusion of individuals who have suffered from hepatitis as blood donors and use of plasma pools prepared only from the blood of a small number of donors.

VIRUSES AND TUMOURS

Animal experiments

Rous sarcoma

About 50 years ago Rous (1911) discovered that a sarcoma of fowls could be transmitted by cell-free filtrates from one fowl to another. Since then his experiments have been amply confirmed and many other virus tumours of animals have been described. At first some pathologists questioned the neoplastic nature of the Rous sarcoma and considered that it should not be classified as a true malignant tumour, but today it is generally accepted that this and the other transmissible virus tumours of animals have no characteristics which set them apart from other tumours except for their known viral aetiology.

Shope papilloma

A further step forward in our knowledge of animal tumours came when Shope (1932) described an infectious papilloma of the cotton-tail rabbit which could be transmitted by tumour filtrates. Inoculation of the virus into the skin of another species, the domestic rabbit (Shope, 1933) also produced papillomas, but with increasing age these benign tumours tended to become carcinomatous. Once the malignant change had occurred virus was no longer recoverable from the tumour, but the tumour cells could be transplanted successfully from one rabbit to another. Even though virus could not be demonstrated in the malignant tumours by the inoculation of filtrates, it was still present. This could be shown by the fact that rabbits receiving carcinoma transplants developed specific neutralizing antibody against the papilloma virus. The obvious deduction which could be drawn from these observations was that though virus was present within the carcinoma cells it was in a latent or masked form.

Several of the more ordinary viruses causing infectious diseases are known to localize and persist in tumour cells without apparently interfering with or aiding tumour growth, and therefore the question arose as to whether the latent papilloma virus was being carried as a passenger or whether it was itself the driving force behind the malignancy of the cells. Do viruses induce malignant change in the

by fits and loss of consciousness and if this possibility is not kept in mind the patient may be diagnosed as having a cerebral tumour, abscess or haemorrhage and be subjected to diagnostic procedures which might aggravate the inflammatory encephalitis.

Hepatitis

Apart from experiments in human volunteers, no one has yet isolated and identified with certainty the viruses of hepatitis. From epidemiological studies there appear to be at least two viruses—hepatitis virus A which is the agent of infectious hepatitis, and hepatitis virus B which is responsible for homologous serum jaundice. Most of the information on these viruses comes from epidemiological studies in human beings.

Virus A is transmitted from person to person by direct or indirect contact with infectious faecal or oropharyngeal excretions. Since the virus is present in the blood in the pre-icteric and icteric stage of the illness transmission may also occur by parenteral inoculations. The incubation period is about four weeks and infections can be endemic or epidemic. The onset is characterized by fever and such symptoms as anorexia, nausea and abdominal discomfort and sometimes tenderness over the liver. Posterior cervical lymphadenopathy is common and there may also be splenomegaly. After a pre-icteric phase of from a few days to a few weeks jaundice appears with a return of gastro-intestinal symptoms and enlargement and tenderness of the liver and spleen. The icteric phase which may last for as long as a month is followed by a rapid and uneventful convalescence in most cases. Death can occur from hepatic coma and in some patients there may be relapses. The ratio of non-icteric to icteric cases is variable and no accurate figure can be given.

Virus B is usually transmitted by the inoculation of human blood or blood products from individuals who are carrying the virus in their blood. The incubation period is from 60 to 160 days, which is the longest incubation period of any known virus disease in man. (A short incubation period associated with inoculations is most likely due to virus A.) The illness is similar to infectious hepatitis although the onset may be more insidious and fever is less common. Because of the long incubation period few patients (or doctors) will tend to associate injections or inoculations which had taken place perhaps more than four months before with the onset of jaundice.

Diagnosis

Differentiation of infection with virus A or B depends on a careful history. During an epidemic or when there is a history of contact a month previously with a known case the diagnosis will be easy, but much more information could be obtained if viral hepatitis was a notifiable disease. The diagnosis in the pre-icteric phase is very difficult because it can mimic the prodromal symptoms of many infectious diseases. The appearance of bilirubin in the urine in the presence of a normal sedimentation rate and tenderness of the liver are perhaps the most important points in making an early diagnosis. The turbidity and flocculation tests may also be positive at this stage. Once jaundice has developed the differential

most interesting because species specificity had usually been considered a characteristic feature of tumour viruses. This is another quality of the SE polyoma virus which is more in keeping with a classical virus than the known tumour viruses.

Application to human malignant disease

It is difficult to judge how much of this work on animal tumours has any bearing on the study of malignant disease in man. Obviously we should be most cautious in drawing too close an analogy between the tumours found in highly inbred stocks of mice and those in man. However, because viruses have without question been shown to induce a variety of malignant tumours, it seems likely that they are primarily or partly responsible for at least some human tumours. Indirect methods of investigation such as the examination of ultra-thin sections of tumour cells under the electron microscope, and the isolation of viruses from tumours *in vitro* may well answer this question which naturally cannot be resolved by the direct methods of inoculation used in animals.

If some human tumours are eventually shown to be caused by viruses how could this knowledge help us in the prevention and treatment of malignant disease? Here again studies of animal tumours are likely to pave the way for advances in human medicine.

Tumour virus immunology

The study of animal tumour virus immunology has been developing rapidly and it is likely to provide us with much information about the natural history of the viruses even if it does not lead to methods of prevention and treatment. For example it has been found that antibody to the SE polyoma virus is present in mice of a number of different stocks, and even in some wild mice. Since the antibody appears to be specific these findings suggest that the polyoma virus may normally exist as a harmless parasite and be responsible for a high incidence of leukaemia only in certain inbred strains of mice like the AK strain. If this is so it raises the important question of whether some of the ordinary infectious viruses which we know as harmless or relatively harmless parasites may not at times act as tumour viruses.

The protective effect of passive immunity has been demonstrated with some tumour viruses and a successful vaccine has apparently been prepared against at least one mouse tumour virus. A preliminary trial of human tumour vaccine has been reported (Graham and Graham, 1959). Their results are difficult to assess, and it would seem that we require more basic information about the immunology of tumours before this type of trial is likely to meet with success.

Chemotherapy

Another possible line of attack on tumour viruses is chemotherapy. At the moment it is not easy to predict whether this form of treatment is ever likely to be effective because the chemotherapy of infectious disease viruses has made little progress. There is a very close association between virus and cell in the case both of tumour viruses and classical viruses, thus the problem of finding a

same way as chemical carcinogens by irreversibly altering the hereditary make-up of the infected cells or is the continued presence of the virus necessary for the maintenance of malignancy? This question, which is of fundamental importance, has yet to be answered.

Bittner's milk factor

One of the next major advances in the study of tumour viruses was the discovery by Bittner (1936) of a virus which caused mammary carcinoma in mice. This virus which he called the "milk factor" was transmitted by the female mice of a certain inbred stock to their offspring via the milk, and months later the mature female offspring suffered from a high incidence of mammary carcinoma apparently caused by the virus. By suitable experiments Bittner was able to show the importance of endocrine factors, genetic constitution and the age at which mice were infected; all of these played a part in determining the incidence of virus induced mammary carcinoma. The discovery of the "milk factor" virus was of the greatest importance. It demonstrated a mechanism whereby malignant tumour viruses might pass naturally from one animal to another, and also the ability of tumour viruses to lie latent for long periods. In addition there was the concept of a virus acting as one of a number of unrelated factors in the stimulation of malignant growth.

Mouse leukaemia

In recent years dramatic advances have been made in the study of mouse leukaemia. These advances stem from the discovery by Gross (1956, 1958) that leukaemia could be induced in mice of one strain (C_3H) if they were inoculated in the first few hours of life with cell-free extracts of leukaemic or normal tissue from another strain of mice (AK) which had a very high incidence of spontaneous leukaemia. As with Bittner's "milk factor" virus there was a latent period of several months before leukaemia appeared. Unlike the Bittner virus the leukaemia virus was not present in milk but it could be found in the tissues of AK strain embryos before birth. From his mouse leukaemia studies, Gross developed his theory of vertical transmission of virus to the offspring *in utero* leading to a hereditary but not a genetic trait in AK mice.

The SE polyoma virus

Another leukaemia virus of mice has been described by Friend (1957a, b) which can be transmitted to adults, but the most remarkable tumour virus is the polyoma virus of Stewart and his colleagues (1957). The SE polyoma virus which is derived from the AK strain of mice can be grown in monkey kidney or mouse embryo tissue culture in which it produces cytopathogenic changes. In this respect it behaves more like the ordinary infectious disease viruses than previously described tumour viruses. Inoculation of tissue-culture-grown virus into newborn mice and hamsters induces a wide variety of tumours. So far 26 different types of tumour have followed inoculation with polyoma virus ; these include sarcomas, epitheliomas and angiomas of various organs. The lack of species specificity shown by the fact that tumours can be induced in hamsters as well as in mice is

from 8 to 11 months after primary inoculation, but a third booster injection gave the majority a substantial antibody rise to each type. There is no doubt that potent Salk-type vaccine confers a high degree of immunity against paralysis but its durability is unknown; antibody, therefore, remains the index of protection. The potency of the vaccines used is not yet known and a satisfactory test is needed. Great variability exists in the different commercial vaccines and, until potency is improved, a fourth inoculation may be required in cases of special risk. Efficient primary immunization, however, seems more satisfactory. Live, attenuated poliovirus vaccines, taken orally, were developed in the belief that immunity would be more lasting. The reports of Kropowski encouraged a small trial in Northern Ireland. Results showed that live polioviruses multiply better in the alimentary tract of children than of adults and suggested preliminary evaluation in triple-negative children. A trial of Cox's strains confirmed that the virus readily spreads from vaccinated persons to contacts and produces slight increase in neurotropism. Definite changes towards neurotropism have been found in children receiving Sabin's type 3 virus. These strains have produced no harmful effects in more than half a million persons, but their exact degree of safety, especially with regard to spread, has not been determined. Their use for large-scale field trials, therefore, is not at present supported by British investigators but is being examined in other countries.

Poliomyelitis

Transportation of severely paralysed patients

MACRAE (1959) discussed the transport of severely paralysed patients, particularly those with impairment of breathing or swallowing. With the increasing incidence of poliomyelitis, respiratory centres have been established. One was inaugurated at Ham Green Hospital, Bristol, for sending assistance, equipment and transport to the patient. The patient's own doctor was asked to telephone the hospital doctors for discussion, an important factor in the service. The first call suggested a dying case of bulbar poliomyelitis. Since the journey was a long one, it was suggested that a locally available anaesthetist inserted an endotracheal cuffed tube and breathed the patient manually on the way. This enabled tracheotomy to be performed on arrival; ventilation was maintained by mechanical positive pressure. The success of this procedure suggested supervision by a local anaesthetist in every case, thus reducing the ambulance personnel and equipment. The latter consists of an adjustable inverted V-frame to support cases with impaired swallowing; manual mask apparatus for breathing insufficiency; and equipment for passing an endotracheal tube in cases with both defects. A few instruments, drugs and an oxygen cylinder are carried. In four years 26 cases have been successfully transported with no ambulance deaths. Once the patient's airway is clear and ventilation established, he can safely be transported long distances.

Assessment of respiratory failure

WALLEY (1959) assessed respiratory failure in poliomyelitis. This may occur either by paralysis of the intercostal muscles and diaphragm or by obstruction of the airway from paralysis of the muscles concerned with swallowing, the most important feature of spinal bulb involvement. Failure of swallowing is diagnosed clinically by the pooling of pharyngeal secretions. Failure of respiration is considered in terms of respiratory function which must be tested. Function tests are, however, impracticable in patients under six years, but if they have no arm weakness, can cry loudly and sleep soundly, they do not generally need artificial respiration. Spirometry is the most valuable technique for assessing respiratory function. Other methods include estimation of arterial blood gases and of end tidal carbon dioxide content, chest radiography and pressure measurements. When swallowing fails, measurement of vital capacity is difficult and a face-mask must be substituted for the mouthpiece of the spirometer. Partial collapse of the lung may occur, increasing the ventilatory requirements and decreasing ability. To detect this, chest radiography is used with blood-gas analysis if necessary. Possible damage to the respiratory centre may be diagnosed by irregularity in rate and depth of breathing.

substance which will destroy or inhibit the virus without also having an adverse effect on normal cells is difficult.

Conclusion

Animal tumour virus research has led to many fascinating and possibly relevant discoveries but it would be wrong to hope that because of these discoveries any solution to the problem of malignant disease in man is round the corner. About the year 1910 the viral aetiology of poliomyelitis was discovered, but nearly half a century elapsed before an effective means of prevention was found, and to this day no specific treatment for the acute disease is available. The first virus-induced malignant tumour of man has yet to be discovered, let alone the means of preventing or treating it.

REFERENCES

Bittner, J. J. (1936). *Science*, **84**, 162.
Carter, A. B. (1951). *Brit. med. J.*, **1**, 987.
Favre, M., and Hellerstrom, S. (1954). *Acta dermato-venereal. Stockh.* (Suppl. 30), **34**, 1.
Friend, C. (1957a). *J. exp. Med.*, **105**, 307.
— (1957b). *Ann. N. Y. Acad. Sci.*, **68**, 522.
Graham, J. B., and Graham, Ruth M. (1959). *Surg. Gynec. Obstet.*, **109**, 131.
Gross, L. (1956). *Cancer*, **9**, 778.
— (1958). *Cancer Res.*, **18**, 371.
King, A. J. (1959). *Brit. med. J.*, **2**, 1396.
Knight, G. C. (1957). *Postgrad. med. J.*, **33**, 448.
Macrae, J. (1959). *Med. J. Sthwest.*, **74**, 45.
Rous, P. (1911). *J. Amer. med. Ass.*, **56**, 198.
Russell, W. R. (1958). *Brit. med. J.*, **2**, 222.
Stern, H., Elek, S. D., Millar, D. M., and Anderson, H. F. (1959). *Lancet*, **2**, 871.
Shope, R. E. (1932). *J. exp. Med.*, **56**, 803.
— (1933). *Ibid.*, **58**, 607.
Stewart, S. E., and Eddy, B. E. (1959). *Perspectives in Virology*. Ed. by M. Pollard. p. 42. New York; Wiley.
— — Gochenour, A. M., Borgese, N. G., and Grubbs, B. E. (1957). *Virology*, **3**, 380.
Walley, R. V. (1959). *Brit. med. J.*, **2**, 82.
Wyburn-Mason, R. (1957). *Brit. med. J.*, **1**, 678.

SELECTED ABSTRACTS

Poliomyelitis vaccination

Dick and Dane (1959) discussed vaccination against poliomyelitis in the United Kingdom and described the manufacture of inactive poliovirus vaccines and the tests made to ensure sterility and purity. In January, 1956, the Government announced a poliomyelitis vaccination programme, but the amount of vaccine ultimately available only justified a field trial. Results indicated that it conferred about 80 per cent protection in pre-school and school children. It was then offered to children already registered and, in 1958, to children aged up to 15 years and to expectant mothers, supplies being supplemented from North America. A further extension was made to general practitioners. By December, 1958, 7 million persons had received two primary inoculations. The field study showed that two weeks after the second inoculation, all except 2 of 196 children had produced antibodies to all three types. A decline in antibody occurred in 100 children

in the central zones of the liver lobules, appearing as small granules or clumps in the cytoplasm of damaged cells or as thin plugs lying within biliary canaliculi. Of 85 cases in groups 1 and 2, presenting all the histological features of acute viral hepatitis, only 42 were free of intralobular bile plugs; in 33 cases they were found in the acute stage. A study in relation to phase of the disease showed that in 19 cases intrahepatic bile stasis was more pronounced in the first fortnight after the onset of jaundice; in 8 cases, in the second fortnight. The peak occurred between 5–15 days after jaundice appeared, falling rapidly in the third week and further declining. These findings were confirmed by military cases in which serum bilirubin levels were available. Significant correlation therefore appears to exist between the incidence of intrahepatic bile stasis and serum bilirubin levels. Various mechanisms suggested to explain the presence of clinical jaundice and intrahepatic bile stasis in viral hepatitis, include damage to the liver cell, damage to biliary canaliculi (cholangioles) and obstruction to bile flow, the latter two being generally accepted. They are discounted by the author, however, in view of the conspicuous hepato-cellular necrosis which is a signal feature of the disease. Studies of the dynamics of intrahepatic bile flow show that jaundice is chiefly the result of impairment of liver cells and reflux of bile from disrupted canaliculi. Intrahepatic bile stasis results from failure of the liver cells to secrete adequate bile to maintain its flow. The most significant factor therefore in the pathogenesis of jaundice and intrahepatic cholestasis is damage to the liver cell itself. Cholangiolar damage or obstruction is not involved.

Risk from whole blood and stored plasma

Discussing the prevention of serum hepatitis due to transfusion of plasma, Hoxworth, Haesler and Smith (1959) advocate the use of liquid plasma stored at temperatures of 72°–95°F. If the plasma is stored for a period of six months the average temperature need not be greater than 80·6°F. and there is no need for constant temperature control. Sterility can be maintained without the employment of freezing or ultraviolet rays. Modified Seitz filtration may be used for clarifying the liquid. This type of processing yields a product which is of value for parenteral protein feeding and for rectifying deficits of plasma volume. No cases of hepatitis were observed in a group of 317 patients who were given transfusions of processed plasma. The authors refer to a statistical analysis of a series of recipients of whole blood and state that if whole blood had been employed instead of processed plasma in the management of the group of 317 patients, hepatitis would have developed in 39 cases. The following case history indicates the diagnostic criteria in a patient with serum hepatitis. Icterus developed in a man, aged 37 years, 53 days after the transfusion of whole blood. Laboratory data showed a thymol turbidity of 17·5 units and a total bilirubin of 18·4 milligrams per cent. The prothrombin content was 64 per cent of normal. Twenty days after the onset of jaundice liver biopsy revealed the presence of active viral hepatitis.

Herpes zoster

Involvement of urinary bladder

Meyer, Brown and Harrison (1959) reported on a woman, aged 70 years, with herpes zoster of the sacral area and urinary retention with overflow. The patient began to suffer from pain in the lower part of the back two weeks after her grandchildren had contracted chicken-pox. Examination revealed a patch of vesicles and crusted lesions in the left sacral region. Sharply demarcated by the midline, the rash extended from the level of the fifth lumbar vertebra to a point two centimetres from the anal margin. The affected area corresponded to the second, third and fourth sacral dermatomes. A cystometrogram showed a hypotonic bladder. Cystoscopy was performed and bulbous lesions were observed on the left ureteric ridge. Generalized cystitis was evident six days later. The mucosal reaction was relatively severe on the left side of the bladder. Administration of the parasympathomimetic drug, ambenonium chloride, five milligrams every six hours, soon brought about an improvement in vesical tone and the patient was free from symptoms five weeks after her admission to hospital. Urinary retention secondary

Respiratory failure together with weakness of swallowing indicates the need for tracheotomy. If lung collapse and infection supervene, 50–100 per cent additional ventilation is required and oxygen saturation and carbon dioxide tension must be measured. So long as radiography or clinical observation reveals no lung change, measurement of the tidal air is sufficient to assess the respiratory state. Clinical detection of gross changes in the lung, in oxygen saturation or carbon dioxide levels indicates immediate action. In moderately severe cases, the vital capacity does not fall below 500–700 millilitres, well above resting tidal air. Such patients can breathe on their own after the acute stage, their vital capacity rising rapidly. The exceptions are those with diaphragmatic paralysis. In more severe cases, the patient should be encouraged to breath until respiratory distress becomes evident.

Epidemic myalgic encephalomyelopathy

Hill, Cheetham and Wallace (1959) described an outbreak of epidemic myalgic encephalomyelopathy among the nursing staff of a Durban hospital. In one week, 59 nurses living in hospital were affected. Later, the disease spread to those living out and sporadic cases occurred in the city. Four phases were observed: prodromal, acute, convalescent and chronic. In the first, severe occipital headache was accompanied by extreme lassitude, sore throat, burning eyes, coryza, nausea or vomiting, and severe backache. The acute phase began with sudden weakness and heaviness in the extremities. Stiffness of the neck muscles was associated with severe occipital headache and weakness of the back and abdominal muscles. Paraesthesia or paralysis of the affected limb was common. Convalescence generally lasted from one to three months; relapse was frequent and often severe. Chronic disability from muscle weakness and paralysis persisted after three months in 11 patients. A fever of about 100°C. was present in most cases with a disproportionate tachycardia. Nystagmus was common initially and slight facial muscular weakness occurred in three cases, with patchy diminution of sensation. Striking changes took place in the muscles which were tender and rubbery. Flaccid at first, they became hypertonic within 48 hours. Contraction, difficult to initiate, was slow and clonic, agonists and antagonists contracting simultaneously. Pain was often extreme, with muscle spasm and cramp. Weakness of the back and abdominal muscles with severe pain at the base of the spine became diagnostic. Ten patients had retention of urine with overflow incontinence. Psychiatric changes were predominant and euphoria was an early manifestation. Inability to concentrate, defective memory, drowsiness and instability co-existed with a "belle indifference". The haematological, bacteriological and pathological chemical findings were not abnormal. No virus was isolated. Urine examinations for insecticides were negative. Muscle tests showed no involvement of the muscle or myoneural junction. Treatment is essentially rest in bed. Massage often evokes cramps; antispasmodic drugs are ineffective. The aetiology remains obscure but an infective origin seems likely.

Virus hepatitis

Intrahepatic bile stasis

Dubin (1959) reviewed intrahepatic bile stasis in acute non-fatal viral hepatitis. The prevailing American view is that intrahepatic bile stasis occurs in the subsiding phase of the disease but less commonly in the acute stage. The author, however, in common with a single British investigator, questions this opinion and studies the condition with particular regard to incidence and severity, pathogenesis, phase of the disease, degree of clinical jaundice and serum bilirubin levels. A total of 214 needle biopsy specimens were obtained from 129 random cases at intervals of between several hours and 250 days after onset of jaundice. Eighty-six cases with first biopsy within 15 days were divided into four types. (1) Diffuse necrosis and parenchymal inflammation (classical viral hepatitis). (2) Morphologically the same, but with superimposed bile plugs. (3) Cholestatic hepatitis with slight focal necrosis and parenchymal inflammation. (4) Cholestatic hepatitis with negligible necrosis and inflammation. Stagnant bile was more prominent

Maternal Influenza

COFFEY and JESSOP (1959) give an account of the incidence of influenza among women who attended the antenatal clinics of three maternity hospitals in Dublin. As it was expected that the pandemic of Asian influenza would reach Ireland in October, 1957, plans for the study were prepared in advance. The investigation took place during a period of nine months in 1957–1958 and 663 women gave a history of having suffered from an attack of influenza while pregnant. As compared with a control group these women gave birth to a greater number of children with congenital deformities. The increase was in the ratio 2 4:1 and in most instances the congenital defects were found in the central nervous system. Anencephaly was a relatively common finding in both series. The risk of malformation was greatest when the attack of influenza occurred during the first three months of pregnancy. It was not possible to identify the virus, but Asian influenza was prevalent when the investigation was held. The children born to the two series of women showed a similar sex ratio, and no significant difference was detected in the incidence of stillbirths and prematurity. With reference to the relation between the virus and the congenital deformities, the authors put forward the hypothesis that the defects result from the action of metabolites which cross the placenta. The metabolites may be derived either from the virus or from the damaged mucous membrane of the respiratory tract.

Salivary gland virus disease

NELSON and WYATT (1959) stated that salivary gland virus disease is of world-wide distribution. The size of the virus is believed to be 100 millimicrons. Inactivation of the virus is effected either by heating at 56°C. for 30 minutes or storage for one week at 4°C. Infectivity of the virus is destroyed within two hours when a solution of 20 per cent diethyl ether is added to suspensions of virus. Cytological techniques are of diagnostic value, for intranuclear inclusions may be found in the exfoliated epithelium. After the third or fourth months of pregnancy the virus is transmitted from mother to foetus through the placenta. Cell infection produces changes in the nucleus and cytoplasm. The nuclear inclusions may be 15 microns in width. The cytoplasm is swollen and vacuolated; it contains basophilic and osmophilic structures which measure 2–4 microns in diameter. Only 17 cases of the adult type of disseminated disease have been described in the literature. Mononuclear pneumonitis has been recorded in 14 of these cases. The affected lungs contain rounded areas which range in size from two millimetres to six centimetres in diameter. Microscopically the alveolar cells are prominent and many alveoli are distended by masses of protein coagulum. Dense hyaline membranes may be present. Intrahepatic lesions have been described in eight cases, but viral particles have rarely been observed in the reticulo-endothelial system. In the newborn the lesions may be more extensive than in adults. The brain is attacked in 15–25 per cent of cases. Pronounced changes may be detected in the ependymal lining and subependymal mantle of the lateral ventricles. Gross changes include periventricular calcification, microcephaly, hydrocephalus and micropolygyria. Radiographs of the skull may reveal calcified areas. Birth may be premature and the infant may show signs of jaundice, petechiae and hepato-splenomegaly. Numerous immature leucocytes and red cells may be found in peripheral blood smears. Pulmonary, hepatic or renal insufficiency may ensue, and sometimes severe haemorrhage occurs. Usually the case proves fatal within two weeks of the onset of the disease. In infants aged 2–4 months the first manifestations are diarrhoea and vomiting or symptoms due to infection of the upper respiratory tract. Among this group death usually takes place in 2–8 weeks. A few patients recover from the disease, but the sequelae include severe brain damage, cirrhosis of the liver and pulmonary fibrosis.

Tumours and viruses

Immunological relationships of a filterable agent

FRIEND (1959) discussed immunological relationships of a filterable agent causing leukaemia in adult mice. A neoplastic disease with a leukaemic character was serially

to herpes zoster was also observed in a woman, aged 76 years. In this case the rash appeared on the right buttock and right side of the perineum in the region innervated by the third, fourth and fifth sacral segments. Both patients showed evidence of lepto-meningitis, with increase of lymphocytes in the cerebrospinal fluid. Vesical hypotonia and urinary retention were attributed to a severe inflammatory reaction extending from the dorsal-root area to the meninges and spinal cord.

Herpes simplex

Herpetic whitlow

STERN and his colleagues (1959) reported on 54 nurses with septic fingers. Most of the cases were observed in a neurosurgical unit. Usually the lesion was confined to a single digit, especially the thumb or index finger. There were seven recurrences at the original site within a period of three years. Bacteriological examination of the contents of the whitlows revealed a variety of organisms, including *Staphylococcus pyogenes*, but material obtained from intact vesicles yielded the characteristic cytopathogenic effect of herpes simplex virus. With reference to the epidemiology of the disease, only a few patients were found to be salivary carriers of the virus. On the other hand, during the post-operative phase the respiratory secretions contained virus in 6 per cent of patients. In six instances the infection of the nurses was attributed to handling tracheotomy catheters. Serological tests for neutralizing antibodies revealed that 73 of 149 nurses were susceptible to virus infection. The authors stress the fact that hitherto whitlow has not been recognized as a disease due to herpes simplex. The characteristic lesion shows vesicles which coalesce to produce a honeycombed appearance and much destruction of the superficial tissues. Extension of the process may lead to separation of the nail. No pus is obtained when the digit is incised. Pain is often severe, but fever, constitutional disturbance and regional adenitis are usually minimal. As for prevention of the disease, the nurse should wear rubber gloves when catheter suction is required. Alternatively, the hands should be immersed in cetrimide solution, 1:1000, for several minutes after the catheter is handled.

Congenital abnormalities and virus infections

Rubella and incidence of congenital abnormalities

COFFEY and JESSOP (1959) give an account of a prospective survey of pregnant women during an epidemic of rubella which occurred in Dublin in 1956. Mothers in attendance at the maternity hospitals were asked about their family incidence of rubella. It was found that 26 mothers had suffered from the disease during pregnancy and 49 mothers had been in contact with the disease. Among the babies born to these mothers there were three cases of talipes equinovarus. In addition, three infants showed signs of the following defects, respectively: anencephaly, congenital cataract and congenital heart disease. For the purposes of comparison with a previous survey of the general population of Dublin the case of heart disease was omitted from consideration. Whereas in the first survey the rate for abnormal births was 16 per 1,000 the rate for the second survey was 67 per 1,000. As compared with mothers who were contacts of rubella, mothers infected with the disease had a higher percentage of deformed children. Among the latter group the risk of giving birth to an abnormal infant was greatest when rubella had occurred during the first trimester of pregnancy. During this trimester the risk was 30 per cent as against 12 per cent during the second and third trimesters. Discussing other investigations concerning the association between rubella and congenital deformities the authors point out that estimates of risk based on retrospective surveys have ranged from 40 to 100 per cent. On the other hand, with prospective surveys the results have shown a risk of 10–25 per cent. Even when the lower figures are considered it would seem that certain prophylactic measures are required. Girls should be encouraged to become contacts of german measles and women should avoid contact with the disease during the early months of pregnancy. If contact has occurred an attempt should be made to prevent the development of an attack by the administration of immune serum or *gamma*-globulin.

Maternal influenza

COFFEY and JESSOP (1959) give an account of the incidence of influenza among women who attended the antenatal clinics of three maternity hospitals in Dublin. As it was expected that the pandemic of Asian influenza would reach Ireland in October, 1957, plans for the study were prepared in advance. The investigation took place during a period of nine months in 1957–1958 and 663 women gave a history of having suffered from an attack of influenza while pregnant. As compared with a control group these women gave birth to a greater number of children with congenital deformities. The increase was in the ratio 2·4:1 and in most instances the congenital defects were found in the central nervous system. Anencephaly was a relatively common finding in both series. The risk of malformation was greatest when the attack of influenza occurred during the first three months of pregnancy. It was not possible to identify the virus, but Asian influenza was prevalent when the investigation was held. The children born to the two series of women showed a similar sex ratio, and no significant difference was detected in the incidence of stillbirths and prematurity. With reference to the relation between the virus and the congenital deformities, the authors put forward the hypothesis that the defects result from the action of metabolites which cross the placenta. The metabolites may be derived either from the virus or from the damaged mucous membrane of the respiratory tract.

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Tumours and viruses

Immunological relationships of a filterable agent

FRIEND (1959) discussed immunological relationships of a filterable agent causing leukaemia in adult mice. A neoplastic disease with a leukaemic character was serially

transmissible to adult mice by an agent present in cell-free filtrates prepared from the neoplastic tissue. Antisera capable of neutralizing this agent and an active immunity to the leukaemic effects of the virus were investigated. Adult mice of Swiss breed were used. Four rabbits were immunized and bled 14–21 days later; the sera were then tested. When cell-free material was first found effective in inducing the disease, approximately 20 per cent of the injected mice remained healthy and subsequently immune to an injection of leukaemic material which induced the disease in most of the controls. To determine the source of their immunity, the antigenicity of the agent was investigated. Neutralization tests were made with the antisera of mice and rabbits injected with the agent. Sera from rabbits obtained prior to immunization and from normal mice, served as controls. When the antiserum was mixed with the filtrate, 90 per cent of the mice survived, compared with 16 per cent of the controls. When cells were inoculated intraperitoneally with the antiserum, 60 per cent of the mice survived, compared with 4 per cent of the controls. Antisera prepared in rabbits gave similar results. Further evidence indicating that neutralization of infectivity is produced by specific antiviral antibody was obtained from studies with absorbed antiserum. Neutralization tests performed with sera from normal individuals, leukaemic patients and mice with other neoplasms produced no similar neutralizing antibody. Vaccination against the agent was investigated and it was found that a formalinized vaccine prepared from filtrates of leukaemic spleens induced immunity in approximately 80 per cent of the vaccinated mice. Meanwhile, the specific antiviral response of the leukaemic agent suggests the feasibility of a prophylactic vaccine.

Effect of vaccine on cancer patients

GRAHAM and GRAHAM (1959) described the use of Freund's adjuvant type autogenous vaccines in the treatment of 114 patients suffering from advanced cancer. For the most part the tumours were gynaecological in origin. Treatment was based upon the hypotheses that a part of the tumour differs antigenically from the host and that adjuvants are of value in inducing the immune response. Freund devised an adjuvant which was composed of a light mineral oil, an emulsifying agent and killed mycobacteria. The authors employed the following antigens: whole tumour homogenate, normal saline extract and suspension, cellular suspension and one molar sodium chloride extract. A milky water-in-oil emulsion was prepared by adding antigen to an equal volume of adjuvant and repeatedly drawing the fluid into a syringe and expelling the mixture. Cold abscesses developed in 5 of 25 patients who were injected intramuscularly with the vaccines. Subsequently, therefore, the intradermal route was employed. Complete adjuvants containing killed mycobacteria were used for all first injections. In order to avoid the activation of a pre-existing tuberculous lesion it was considered advisable to use *Mycobacterium butyricum* in preference of *M. tuberculosis*. Thirteen patients died within the first month and the case records of these patients were omitted from the final analysis of the results. Fourteen patients remained well with no demonstrable disease and 55 patients lived for at least seven months. In 8 cases the condition became quiescent. Apparently the results were not influenced by the site of the tumour. The cellular suspension proved to be the most suitable preparation for the vaccine and the best results were obtained in patients who received two injections. Ulceration at the site of the intradermal injection was recorded in 63 of 75 cases. The ulcers healed within 3–4 months. In two instances implants developed at the site of injection. There were no systemic complications. Vaccine therapy seemed to produce increased sensitivity to ionizing radiations. With reference to the vaginal cytological response, an increase in the number of histiocytes and in the sensitization response coincided with the disappearance of symptoms.

A "polyoma" virus derived from a mouse leukaemia

NEGRONI, DOURMASHKIN and CHESTERMAN (1959) reported the isolation of the M.H. polyoma virus in tissue culture from the spleen of a leukaemic AK mouse. The properties of the virus resemble those of the polyoma agent of Stewart and Eddy. Both agents

agglutinate guinea-pig erythrocytes at + 4°C. and are resistant to heat and ether. When inoculation experiments were performed on suckling mice, rats and hamsters it was found that the virus had produced renal sarcomas in hamsters and mammary carcinoma in a mouse. These tumours were serially transplantable. So far as the hamster lesions were concerned, in addition to tumours of the kidney there were multiple sarcomas of the heart and sometimes of the liver, blood-stained peritoneal effusions and haemorrhagic lesions of the liver, uterus and lungs. By infecting fibroblast tissue cultures derived from a mouse embryo the investigators were able to determine the presence of the virus in the hamster tumours. The infected tissue cultures were examined with the electron-microscope. Many particles, 30–40 millimicrons in diameter, were detected in the cell nuclei. The cytoplasm contained larger particles with an external membrane surrounding a central body, but there were more particles in the nuclei than in the cytoplasm.

REFERENCES

Coffey, Victoria P., and Jessop, W. J. E. (1959). *Lancet*, **2**, 935.
— — (1959). *Irish J. med. Sci.*, 397, 1.
Dick, G. W. A., and Dane, D. S. (1959). *Brit. med. Bull.*, **15**, 205.
Dubin, I. N. (1959). *Gastroenterology*, **36**, 645.
Friend, Charlotte (1959). *J. exp. Med.*, **109**, 217.
Graham, J. B., and Graham, Ruth M. (1959). *Surg. Gynec. Obstet.*, **109**, 131.
Hill, R. C. J., Cheetham, R. W. S., and Wallace, H. L. (1959). *Lancet*, **1**, 689.
Hoxworth, P. I., Haesler, W. E. Jnr., and Smith, H. Jnr. (1959). *Surg. Gynec. Obstet.* **109**, 38.
Macrae, J. (1959). *Med. J. Sthwest.*, **74**, 45.
Meyer, R., Brown, H. P., and Harrison, J. H. (1959). *New Engl. J. Med.*, **260**, 1062.
Negroni, G., Dourmashkin, R., and Chesterman, F. C. (1959). *Brit. med. J.*, **2**, 1359.
Nelson, J. S., and Wyatt, J. P. (1959). *Medicine*, **38**, 223.
Stern, H., Elek, S. D., Millar, D. M., and Anderson, H. F. (1959). *Lancet*, **2**, 871.
Walley, R. V. (1959). *Brit. med. J.*, **2**, 82.

INDEX

NOTER-UP, 1960

The Key Numbers in the margins correspond to those in the main volumes, in which they appear at the top left-hand corner of each right-hand page.

Vol. 1

KEY NO.

New Heading **ABDOMEN**

Article

The alimentary system [1957], p. 61

1 **ABDOMINAL EMERGENCIES**

Abstracts

Intestinal rupture following non-penetrating injury [1951], p. 269
Perforation of the rectum [1951], p. 269
Primary inflammation of the appendices epiploicae [1951], p. 269
Closed abdominal injuries: value of early surgical exploration [1955], p. 216
Laceration of the superior mesenteric artery: treatment [1955], p. 216

2 **ABDOMINAL PAIN**

Abstract

Mesenteric cyst: aetiology and treatment [1951], p. 270

3 **ABDOMINAL WALL**

Abstracts

Retroperitoneal tumours: classification as a guide to clinical diagnosis [1955], p. 217
Extraperitoneal pneumography in diagnosis of retroperitoneal tumours [1955], p. 217
Surgical treatment of retroperitoneal tumours [1955], p. 218
Congenital deficiency of abdominal musculature: obstructive uropathy [1960], p. 364

4 **ABORTION**

Article

Abortion [1957], p. 228

Abstract

Threatened abortion: ambulation [1959], p. 208

5 **ABSCESS**

Article

Treatment of the acute abscess [1959], p. 379

6 **ACHLORHYDRIA AND APPETITE**

No further references

Vol. 1

KEY NO.

12 ADRENAL GLANDS (*cont.*):

Abstracts (cont.):

Cushing's syndrome: management and metabolic aspects of adrenalectomy [1959], p. 136
Cancer of the adrenal cortex: natural history, prognosis and treatment [1959], p. 137
Primary aldosteronism [1959], p. 137

13 AFTER-CARE—INTRODUCTION

No further references

14 AFTER-CARE—FOLLOW-UP

No further references

15 AFTER-CARE—METHODS AND VALUE OF MASSAGE

No further references

16 AFTER-CARE—ON RETURN HOME

No further references

17 AFTER-CARE—POST-OPERATIVE

Articles

Early ambulation in the post-operative management of general surgical patients [1955], p. 182
Post-operative chest complications [1957], p. 99

Abstracts

Pain prevention: Efocaine administration [1953], p. 274
Water retention: causative factors [1954], p. 248
Water and electrolyte balance: control following operation [1955], p. 219
Circulation after operation: study and correction of variations [1955], p. 220

18 AFTER-CARE—REMEDIAL AND OCCUPATIONAL THERAPY AND REHABILITATION

Article

Recuperation after operation [1955], p. 114
- Rehabilitation in industry [1955], p. 115
- The programme of rehabilitation [1955], p. 115
- Rehabilitation after meniscectomy [1955], p. 123

Vol. 1

KEY NO.

7 ACIDOSIS

Article

Fluid and electrolyte balance [1953], p. 91

8 ACTINOMYCOSIS

Abstracts

Facial and cervical: treatment [1953], p. 273
Pulmonary: treatment [1953], p. 273

9 ADHESIONS AND CICATRICIAL STENOSES

Abstract

Duodenum: obstruction distal to ampulla of Vater [1956], p. 263

10 ADHESIONS (PLEURAL) IN PULMONARY TUBERCULOSIS

No further references

11 ADIPOSITY

No further references

12 ADRENAL GLANDS

Articles

Adrenalectomy [1955], p. 46
The adrenals [1957], p. 150
The adrenal glands [1959], p. 130

Abstracts

Phaeochromocytoma: bilateral case and new diagnostic tests [1951], p. 270
Endocrine effects of the adrenal glands [1952], p. 205
Cushing's disease: remission following adrenalectomy [1952], p. 205
Chromaffin tumour in a case of arterial hypertension [1952], p. 205
Medullary and cortical tumours: diagnosis and treatment [1952], p. 206
Hypofunction and hyperactivity: hazards in anaesthesia and surgical operations [1953], p. 273
Phaeochromocytoma: adrenaline and noradrenaline effect on the benzodioxane test [1953], p. 274
Total bilateral adrenalectomy: cortisone and glycyrrhizin [1954], p. 248
Cushing's syndrome: treatment [1955], p. 218
Medullary phaeochromocytoma: clinical manifestations and surgical treatment [1955], p. 219
ACTH, cortisone and hydrocortisone in surgery [1956], p. 263
Neuroblastoma in childhood: surgical management [1956], p. 264
Adrenalectomy: hormone replacement therapy [1957], p. 172
Adrenal cortical insufficiency: surgery and the chronically ill patient [1957], p. 174
Adrenaline and noradrenaline: plasma levels in varying conditions of stress [1957], p. 174

Vol. 1

KEY NO.

24 AMPUTATIONS (*cont.*):

Abstracts

Ischaemia of the leg treated by amputation [1952], p. 207
Arteriosclerosis: clinical history and pathology of limb [1954], p. 249
Hemipelvectomy [1954], p. 249
Knee disarticulation: advantages over thigh amputation [1955], p. 220
Choice of technique in senile gangrene [1955], p. 220
Syme's amputation: factors making for success or failure [1957], p. 203
Double above-knee amputation: rehabilitation of the elderly patient [1959], p. 188
Syme's amputation: evaluation [1959], p 188
Lower extremity amputations for arteriosclerosis [1959], p. 189
Tumours of the bony pelvis: resection and radical amputation [1959], p 189

25 AMYLOID INFILTRATION (AMYLOIDOSIS)

No further references

26 ANAESTHESIA—GENERAL

Articles

Anaesthesia [1952], p 127
Anaesthesia—recent advances in pre-operative and post-operative medication [1955], p. 161
Anaesthetic advances [1957], p. 337

Abstracts

Cyclopropane: effects of raised airway pressure during [1952], p. 208
Complications of endotracheal anaesthesia; laryngeal sequelae [1952], p. 208
Relaxants: abnormal sensitivity to [1953], p. 275
Controlled hypotension [1954], p. 250
Effects on blood-sugar [1954], p. 250
Major operations on exsanguinated patients: anaesthetic technique [1955], p. 221
Analgesia in the treatment of compression fractures: technique [1955], p. 221
Application of anaesthesia to diagnostic urology: toxic reactions [1955], p. 222
Pethidine: venous reactions [1955], p. 222
Induced hypothermia: advantages and dangers [1956], p. 264
Controlled hypothermia: indications and results [1956], p. 264
Caesarean sections and vaginal deliveries: use of thiopental [1956], p. 265
Deaths associated with anaesthesia: report on 1,000 cases [1957], p. 347
Cardiac arrest and resuscitation [1957], p. 348

Vol. 1

KEY NO.

19 AIR PASSAGES

Articles

Reconstruction of the trachea, hypopharynx and cervical oesophagus [1951], p. 193
Pulmonary cysts [1957], p. 92
Tracheostomy [1957], p. 98

20 ALLERGY

Abstract

Manifestations following procaine penicillin injection [1952], p. 206

21 AMOEBIASIS—AMOEBIC INFECTION OF INTESTINE (PATHOLOGY)

No further references

22 AMOEBIASIS—AMOEBIC INFECTIONS OF INTESTINE (SURGERY)

No further references

23 AMOEBIASIS—LIVER ABSCESS AND PATHOLOGY OF AMOEBIASIS OTHER THAN INTESTINAL

Abstracts

Comparison of chloroquine and emetine treatment [1952], p. 207
Non-hepatic secondary amoebiasis: diagnosis [1952], p. 207

24 AMPUTATIONS

Articles

Pain—painful stumps and phantom limbs [1951], p. 12
The interinnomino-abdominal amputation [1955], p. 81
Amputations for vascular disease [1957], p. 121
Progress in amputations [1959], p. 180
- Sites of election [1959], p. 180
- Disarticulation at the knee [1959], p. 181
- Disarticulation of the ankle (Syme's amputation) [1959], p. 182
- Amputations for removal of congenitally malformed extremities [1959], p. 182
- Amputations for trauma or disease in children [1959], p. 182
- Preparation for artificial lower limb [1959], p. 183
- Prostheses [1959], p. 184

Vol. 1

KEY NO.

New Heading **ANTIBIOTICS**

Articles

Antibiotics [1954], p. 183
The control of surgical infections with antibiotics [1957], p. 30

Abstracts

Elective abdominal surgery: routine use of antibiotics [1957], p. 55
Pre-operative sterilization of the colon: comparison of antibacterial agents [1957], p. 55
Resistant organisms and chemotherapeutic sensitivity: problems in surgery [1957], p. 56
Novobiocin: clinical and bacterial evaluation [1957], p. 57
Evaluation in staphylococcus pyogenes infections [1957], p. 58
Vancomycin: laboratory and clinical experience [1957], p. 58

33 **ANUS, ARTIFICIAL (MANAGEMENT)**

No further references

34 **ANXIETY STATES**

No further references

35 **APPENDICITIS, ACUTE**

Article

Appendicitis and peritonitis [1951], p. 32

Abstract

Appendicectomy: reduction in mortality rate [1955], p. 223

36 **APPENDIX—TUMOURS OF**

Article

Argentaffinoma [1957], p. 69

Abstract

Adenocarcinoma of appendix: symptoms and signs [1954], p. 251

37 **ARTERIES**

Articles

Progress in arterial surgery [1951], p. 209
Arterial grafting [1953], p. 1
Abdominal aortography [1955], p. 1
Progress in vascular surgery [1957], p. 114

Abstracts

Thrombo-angiitis obliterans of renal artery [1952], p. 210
Physiology and relief of traumatic arterial spasm [1952], p. 210
Aneurysm: resection of descending thoracic aorta [1952], p. 210

'ol. 1

EY NO.

26 ANAESTHESIA—GENERAL (*cont.*):

Abstracts (*cont.*):

Anaesthetic explosions: report of working party [1957], p. 348
Fluothane: investigation into properties [1957], p. 349
Hypothermia [1957], p. 350
Surface cooling for use in open heart surgery [1957], p. 350
Veno-venous cooling [1957], p. 351
Application to surgery [1957], p. 351
Cardiac effects of hypotensive drugs and muscle relaxants [1957], p. 352
Effects of neurophysiology [1957], p. 352

27 ANAESTHESIA—LOCAL

No further references

28 ANAESTHESIA—REGIONAL

Abstract

Transvaginal pudendal nerve block: improved approach [1957], p. 238

29 ANAESTHESIA—SPINAL

Abstract

Results of continuous caudal analgesia in 12,000 deliveries [1951], p. 271

New Heading ANAL DISEASES

Article

Critical review of rectal surgery [1959], p. 78
Immediate skin cover in minor rectal surgery [1959], p. 78
Anal fissure [1959], p. 82

30 ANGINA PECTORIS

Abstracts

Resection of afferent pathway [1954], p. 251
Stellate ganglion block [1956], p. 266

31 ANGIOMA

Abstracts

Diathermy treatment of haemangioma and lymphangioma [1952], p. 209
Surgical removal [1952], p. 209

32 ANTHRAX

Abstract

Chloramphenicol in treatment of cutaneous anthrax [1952], p. 209

Vol. 1

Vol. 1

KEY NO.

37 ARTERIES (*cont.*):

Abstracts (*cont.*):

l. 1
NO.

Vol. 1

KEY NO.

37 **ARTERIES** (*cont.*):

Abstracts (*cont.*):

1

NO.

Vol. 1

KEY NO.

39 **ARTIFICIAL LIMBS** (*cont.*):

Abstracts

Preparation of stump for artificial limb: leg pylons [1952], p. 212
Upper-extremity prostheses: age of fitting in children [1959], p. 187

40 **ARTIFICIAL PNEUMOTHORAX**

Abstract

Pulmonary function: assessment before and after segmental resection [1957], p. 106

41 **ASEPSIS AND ANTISEPSIS**

Article

Antibiotics [1951], p. 19

42 **ASYMMETRY**

No further references

43 **AUTONOMIC NERVOUS SYSTEM: INTRODUCTION**

Abstracts

Clinical manifestations of autonomic dysfunction [1951], p. 276
Transmission of stimuli to effector organs: the chemical concept [1951], p. 276

44 ***AUTONOMIC NERVOUS SYSTEM: ANATOMY***

Article

Anatomy of the autonomic nervous system [1951], p. 39

45 **AUTONOMIC NERVOUS SYSTEM: ARTERIES**

Articles

Obliterative arterial disease [1951], p. 214
Raynaud's disease [1951], p. 216
Primary Raynaud's disease: observations on its aetiology and treatment [1960], p. 22
- Aetiology [1960], p. 23
- *The vascular abnormality [1960], p. 26*
- The sympathetic nervous system [1960], p. 30
- *Investigations of the sympathetic nervous system [1960], p. 31*
- Vasoconstrictor substances in Raynaud's disease [1960], p. 36
- *Endocrine and metabolic studies [1960], p. 38*
- Treatment [1960], p. 41

Abstracts

Indications for, and results of, surgery [1951], p. 277
Blindness due to vascular occlusion: treatment by stellate-ganglion block [1952], p. 212
Posterior upper thoracic sympathectomy: improved method of approach [1956], p. 269

Vol. 2

KEY NO.

46 BACKACHE

Abstracts

Low back and sciatic pain: treatment by hydrocortisone injection [1957], p. 200

Low back pain: experimental investigation into intervertebral disc pressures [1957], p. 207

47 BACTERAEMIA

No further references

48 BACTERIOLOGY

Abstracts

Newborn infants: carriage rates and antibiotic resistance of staphylococci [1955], p. 230

Cross-infection in hospital wards: reduction by suppression of dust on floors and bedclothes [1955], p. 230

Study of antiseptic hand cream in the control of cross-infection [1955], p. 231

Prevention of cross-infection by treatment of carriers [1955], p. 231

Bacteriology of the portal vein: investigations by an original method [1957], p. 134

49 BASAL METABOLISM

Abstract

Interferometric studies [1952], p. 212

50 BEDS, PLASTER

No further references

51 BEDSORES

No further references

52 BIOCHEMICAL TESTS—CURVES AND CHARTS

Abstract

Functional changes in the liver following surgery for portal hypertension: metabolic effects [1955], p. 232

53 BITES AND STINGS

No further references

Vol. 2

KEY NO.

54 BLADDER—INFECTIONS

55 BLADDER INJURIES

56 BLADDER—NEUROGENIC DISTURBANCES

57 BLADDER—POUCHES

58 BLADDER—TUMOURS

Vol. 2

KEY NO.

58 BLADDER—TUMOURS (*cont.*):

Abstracts (cont.):

59 BLINDNESS—MANAGEMENT OF

No further references

60 BLOOD AND BLOOD-FORMING ORGANS: BLOOD EXAMINATION

Article

Abstracts

61 BLOOD PRESSURE: HIGH AND LOW

Articles

Abstracts

Vol. 2

KEY NO.

Vol. 2

KEY NO.

64 BOILS, CARBUNCLES, FURUNCULOSIS

No further references

65 BONE GRAFTING

Abstracts

Malformation of the jaws: co-ordinated methods of treatment [1955], p. 236
Bone regeneration: the two osteogenetic phases [1957], p. 209
Bone fixation: electrolysis and the use of stainless steel [1957], p. 209
Homogeneous epiphyseal-cartilage grafts: experimental study [1957], p. 211

66 BONES—ACUTE AND CHRONIC INFECTIONS

Article

Acute infections of bone [1951], p. 91

Abstracts

Diagnosis and treatment of osteitis pubis [1951], p. 280
Osteitis pubis of non-haematogenous origin [1951], p. 281
Osteosclerosis: aetiology, diagnosis and treatment [1953], p. 278
Osteomyelitis: treatment [1953], p. 279
Osteomyelitis and chondritis: treatment [1953], p. 279
Thiemann's disease: clinical picture [1955], p. 237
Osteomyelitis: treatment by cancellous bone grafts [1955], p. 237
Bone lesions: localization of radioactive gallium [1957], p. 208

67 BONES—ERRORS OF DEVELOPMENT AND GROWTH

Abstracts

Polyostotic fibrous dysplasia [1952], p. 217
Symptoms of infantile hyperostosis [1953], p. 279
Congenital posterior angulation of the tibia with talipes calcaneus [1960], p. 19

68 BONES—METABOLIC DYSTROPHIES

Abstracts

Changes in the jaws in generalized skeletal disease [1952], p. 217
Leontiasis ossia: clinical picture and pathology [1954], p. 257
Porotic and malacic conditions of bone: histopathology [1955], p. 238
Bone metabolism: effect of diet on mobilization of strontium from the rat skeleton [1957], p. 208

69 BONES—NEW GROWTHS

Article

A survey of the biological properties of tumours of bone [1959], p. 157
- Incidence [1959], p. 157
- Classification [1959], p. 159
- Aetiology [1959], p. 164
- Tissue culture and transplantation [1959], p. 170
- Histogenesis [1959], p. 171

Vol. 2

KEY NO.

61 **BLOOD PRESSURE: HIGH AND LOW** (*cont.*):

Abstracts (*cont.*):

62 **BLOOD TRANSFUSION—PRACTICE**

Articles

Abstracts

63 **BLOOD TRANSFUSION—THEORY**

Abstracts

Vol. 2

KEY NO.

72 BRAIN—CONGENITAL DEFECTS

No further references

73 BRAIN—FUNGUS

No further references

74 BRAIN—INJURIES AND COMPLICATIONS

Articles

Brain—spontaneous intracranial haemorrhage [1956], p. 1
The management of acute head injuries [1958], p. 266
General considerations [1958], p. 266
Chest complications [1958], p. 269
Treatment [1958], p. 270
Nutrition and metabolic disorders [1958], p. 274
Metabolic disorders [1958], p. 276
Relation of metabolic disorders to brain injury [1958], p. 279
Hypothermia [1958], p. 279
Cerebral compression [1958], p. 281
Cerebrovascular complications [1958], p. 286
Multiple injuries [1958], p. 288
Management [1958], p. 289
Results [1958], p. 290

Abstracts

Concussion and haemorrhage: aetiology [1952], p. 221
Mechanics of cerebral trauma [1952], p. 221
Visual disturbances [1952], p. 222
Relation of injury to subsequent brain tumour and neural sclerosis [1952], p. 222
Major closed head injuries [1954], p. 258
Acute epidural haematoma of the posterior fossa: treatment [1955], p. 239
Extradural haemorrhages of the posterior fossa: classification and clinical features [1955], p. 239
Subacute and chronic subdural haematoma: treatment [1955], p. 239
Posterior fossa haematoma: case reports [1956], p. 273
Head injury: delayed complications [1956], p. 273
Extradural haemorrhage: mortality rate [1956], p. 273
Postconcussion syndrome [1958], p. 333
Salt retention and uraemia [1958], p. 333
Mortality of head injuries: role of respiratory insufficiency [1958], p. 334
Acute renal failure following head injury: management [1958], p. 334
Spontaneous subarachnoid haemorrhage [1958], p. 336

75 BRAIN—NEUROLOGICAL INVESTIGATION AND SPECIAL TESTS

Article

Surgical treatment of involuntary movements [1954], p. 55

Vol. 2

KEY NO.

69 **BONES—NEW GROWTHS** (*cont.*):

Abstracts

70 **BRACHIAL PLEXUS**

Articles

Abstract

71 **BRAIN—ABSCESS**

Abstracts

Vol. 2

KEY NO.

76 BRAIN—TUMOURS AND TECHNIQUE (*cont.*):

Abstracts (cont.):

Extradural haematoma: differential diagnosis [1953], p. 283
Meningioma: aetiology [1953], p. 283
Medulloblastoma: diagnosis, treatment and end-results [1953], p. 284
Posterior fossa dermoid cysts: aetiology [1953], p. 284
Acoustic neuromas in children: two case reports [1955], p. 240
Hydrocephalus: urinary phenolsulphonphthalein excretion test [1958], p. 343
Thrombosis of internal carotid artery: treatment by arterial surgery [1958], p. 343
Astrocytoma: long-term follow-up [1958], p. 341
Brain tumour: use of tantalum powder as indicator [1958], p. 342
Hypothermia: interruption of carotid or carotid and vertebral circulation [1958], p. 337
Intracranial meningiomas: recurrence after surgical treatment [1958], p. 338
Pearly tumours: in relation to the central nervous system [1958], p. 339
Intracranial tumours: cranial radiography [1958], p. 336
Rathké-pouch tumours [1958], p. 339
Tumours of the thalamus [1959], p. 302
Cerebral tumours: hypothermia in surgical treatment [1959], p. 302

New Heading BRAIN—VASCULAR ANOMALIES

Article

The surgical treatment of ruptured intracranial aneurysm [1959], p. 270
Aneurysms of the intracranial internal carotid artery [1959], p. 272
Middle cerebral artery aneurysms [1959], p. 276
Aneurysms of the anterior communicating artery [1959], p. 278
Aneurysms of the anterior cerebral artery [1959], p. 279
Aneurysms of the vertebral-basilar system of arteries [1959], p. 280
Hypothermia in operation for ruptured aneurysm [1959], p. 280

Abstracts

Intracranial aneurysm [1956], p. 274
Intracranial aneurysm [1959], p. 296
Intracranial arteriovenous aneurysms [1959], p. 297
Effect on the cardiovascular system [1959], p. 297
Cerebral arteriovenous aneurysms: surgical management [1959], p. 298
Cerebral arteriovenous anomalies: intracranial haemorrhage [1959], p. 298
Spontaneous intracranial haemorrhage: surgical treatment [1959], p. 299
Subarachnoid haemorrhage: management [1959], p. 299
Results of treatment [1959], p. 300
Basilar artery insufficiency: radiographic diagnosis and surgical treatment [1959], p. 300
Thrombosis of internal carotid artery [1959], p. 303

Vol. 2

KEY NO.

75 **BRAIN NEUROLOGICAL INVESTIGATION AND SPECIAL TESTS** *(cont.)*:

Abstracts

New Heading **BRAIN—PSYCHIATRIC DISORDERS**

Articles

Abstracts

76 **BRAIN—TUMOURS AND TECHNIQUE**

Article

Abstracts

Vol. 2

KEY NO.

77 BREAST—CARCINOMA OF (*cont.*):

Abstracts (cont.):

Methods of spread of mammary cancer [1956], p. 274
Intracranial metastases from breast cancer [1957], p. 173
Adrenalectomy and hypophysectomy in advanced breast cancer: a comparative study [1957], p. 173
Cancer of the breast: application of research in physiology [1957], p. 252
Characteristics of adrenal-dependent cancers [1957], p. 253
Role of histology in treatment [1957], p. 253
Control of cancer mortality [1957], p. 254
Comparison of treated with untreated cancer [1957], p. 254
Involvement of internal mammary lymph nodes [1957], p. 255
Super-radical mastectomy [1957], p. 255
Radical mastectomy with *en bloc* in continuity resection of the internal mammary lymph node chain [1957], p. 256
Bilateral adrenalectomy and oophorectomy for advanced cancer [1957], p. 256
Adrenalectomy [1957], p. 257
Hypophysectomy in treatment of advanced disease [1957], p. 257
Co-existence with pregnancy [1957], p. 258
Malignant lesions of the nipple [1957], p. 258
Mean clinical value [1957], p. 260
Hormone-dependent breast cancer: application of physiological principles [1959], p. 264
Tumour autonomy in breast cancer: recognition of the hormone-stimulated tumour [1959], p. 265
Hormone assay [1959], p. 266
Effect of oophorectomy [1959], p. 266
Correlation of clinical results with oestrogen production [1959], p. 267
Adrenalectomy: correlation of clinical results with oestrogen production [1959], p. 267
Hypophysectomy: correlation of clinical results with oestrogen production [1959], p. 267
Effect of hypophysectomy [1959], p. 268
Hypophysectomy combined with intrasellar irradiation [1959], p. 268
Cancer of the breast: radioisotope therapy of internal mammary lymph nodes [1959], p. 376

78 BREAST—CARCINOMA OF, POST-OPERATIVE RADIOTHERAPY

No further references

79 BREAST—CHRONIC MASTITIS

Article

Innocent lumps in the breast [1951], p. 100

Vol. 2

KEY NO.

77 BREAST—CARCINOMA OF

Vol. 3

KEY NO.

84 CAESAREAN SECTION

Article

Abnormal presentation [1957], p. 229

Abstracts

Cystographic studies in placenta praevia [1951], p. 288
Caesarean section: mortality [1957], p. 237
Oxygenation of the foetus [1958], p. 224
Rupture of the uterine scar [1958], p. 225
Foetal distress [1958], p. 225

New Heading

CANCER

Article

A cancer records bureau [1960], p. 57
National registration [1960], p. 57
Cancer registration in a regional bureau [1960], p. 60
Other centres in England and Wales [1960], p. 74
Reports [1960], p. 75

Abstract

Surgical treatment of cancer: prophylactic and adjuvant use of nitrogen mustard [1960], p. 104

New Heading

CARCINOID

Article

Carcinoid tumours [1960], p. 78
5-Hydroxytryptamine [1960], p. 78
Carcinoid tumours [1960], p. 81
Pathology [1960], p. 82
Symptomatology [1960], p. 88
The flushing syndrome [1960], p. 89
Diagnosis [1960], p. 94
Treatment [1960], p. 94

Abstracts

Carcinoid syndrome: effect of phenylacetic acid [1960], p. 99
Resection of secreting carcinoid: relief of flushing [1960], p. 100
Vasomotor reactions secondary to malignant carcinoid: control by massive liver resection [1960], p. 100
Metastatic carcinoid disease: development of valvular lesions [1960], p. 100
Vasculocardiac syndrome [1960], p. 101
Carcinoid of the ampulla of Vater [1960], p. 101
Carcinoid tumours of the rectum: clinical study [1960], p. 102

85 CAROTID BODY

Article

The syndrome of the carotid sinus [1953], p. 60

Vol. 2

KEY NO.

80 BREAST—INFECTIONS

Article

Advances in the study of diseases of the breast [1957], p. 245

Abstracts

Mammotrophic potency of human urine: pre-menopausal women [1957], p. 259
Normal post-menopausal women [1957], p. 260

81 BRONCHIECTASIS

Abstracts

Sloughs of the tracheal mucosa associated with bronchiectasis [1951], p. 288
Aqueous contrast media in bronchography [1952], p. 226
Bronchography in infants and very young children [1952], p. 227
Resection in treatment of bronchiectasis [1956], p. 274
Bronchiectasis: pulmonary resection [1957], p. 107

82 BURNS AND SCALDS

Articles

Treatment of burns [1952], p. 38
The treatment of burns in the casualty department [1959], p. 386

Abstracts

Stress response in severe burns [1952], p. 227
Renal function studies [1952], p. 228
Burn wounds in children [1952], p. 228
Homografts: effect of cortisone [1952], p. 228
Homologous grafts: effects of cortisone and ACTH [1952], p. 229
ACTH therapy: clinical and experimental evaluation [1952], p. 229
Disinfection: penicillin, dibromopethamidine, terramycin, and aureomycin [1952], p. 229
Enzymatic debridement [1952], p. 230
Management of patient with second-degree burns [1953], p. 285
Effect of ACTH on skin grafts in third-degree burns [1953], p. 286
Flash burns: classification of degree [1953], p. 286
Ocular burns: corrosion caused by quick-lime [1953], p. 286
Burns: treatment of neglected burn [1954], p. 259
Severe and extensive burns: influence of modern techniques and drugs on survival rate [1955], p. 242
Treatment by exposed and closed methods [1955], p. 242
Methods of treatment according to degree [1955], p. 243
Burns: amino acid loss in urine [1956], p. 275

83 BURSAE

Abstract

Tuberculous subdeltoid bursitis: two case reports [1955], p. 243

Vol. 3

KEY NO.

92 CICATRICES, INCLUDING KELOID

No further references

93 CIRCUMCISION

No further references

94 CISTERNAL PUNCTURE

No further references

95 COAGULANTS AND ANTICOAGULANTS

Article

Abstracts

96 COLIC

No further references

97 COLITIS

Articles

Vol. 3

KEY NO.

New Heading **CARPAL TUNNEL SYNDROME**

Article

The carpal tunnel syndrome [1958], p. 324
- Clinical features [1958], p. 325
- Special tests [1958], p. 327
- Differential diagnosis [1958], p. 328
- Pathogenesis [1958], p. 330
- Treatment [1958], p. 330

Abstracts

Electrical signs in diagnosis [1958], p. 344
Acroparaesthesia and the carpal tunnel syndrome [1958], p. 345
Acroparaesthesia: clinical features [1958], p. 345
Carpal tunnel syndrome in pregnancy [1959], p. 208

86 **CELLULITIS, LYMPHANGITIS, ERYSIPELAS**

Abstract

Lymphangitis: treatment of lymphoedema [1955], p. 244

87 **CELLULITIS—PELVIC**

No further references

88 **CERVICAL RIB AND THE SCALENUS SYNDROME**

Article

Cervical rib and the scalenus syndrome [1958], p. 318
- Anatomy [1958], p. 318
- Costoclavicular compression [1958], p. 320
- Differential diagnosis [1958], p. 321
- Operative treatment [1958], p. 322

89 **CHEMICAL WARFARE—SURGICAL ASPECTS OF**

No further references

90 **CHEMOTHERAPY**

Article

The chemotherapy of malignant diseases [1953], p. 256

Abstract

Chemotherapy in cancer: present status of the postulates of Koch [1955], p. 244

91 **CHORDOMA**

Abstracts

Sacro-coccygeal chordoma and chordoma in other areas [1951], p. 288
Thoracic chordomas [1952], p. 230
Chordoma: staining reactions [1959], p. 178

Vol. 3

KEY NO.

99 COLON—DEVELOPMENTAL ABNORMALITIES AND MEGACOLON

Article

Hirschsprung's disease [1951], p. 163

Abstracts

Hirschsprung's disease: treatment; colectomy and ileo-anostomy [1954], p. 261

Megacolon and associated bladder dysfunction: elimination as a postoperative complication [1956], p. 277

Radiological investigation of megacolon and bladder abnormality [1956], p. 277

100 COMPENSATION, DAMAGES AND PENSIONS

No further references

101 CONJUNCTIVA—DISEASES AND INJURIES

Abstracts

Aetiology of angular conjunctivitis [1952], p. 232

Appearance and differential diagnosis of implantation cyst following injury [1953], p. 289

102 CONSTIPATION

No further references

103 CONTRACTURES

Abstract

Torticollis: breech delivery as causative factor [1955], p. 247

104 CORNEA—DISEASES AND INJURIES

Articles

The surgery of corneal grafts [1953], p. 242

Progress in corneal graft surgery [1959], p. 304

- Control of infection [1959], p. 304
- Technique [1959], p. 305
- Selection of cases [1959], p. 309
- Causes of failure [1959], p. 313
- The donor graft [1959], p. 315

Abstracts

Cortisone in treatment of interstitial keratitis [1952], p. 232

Bullous keratitis: treatment by neurectomy [1952], p. 233

Efficacy of streptomycin in experimental and clinical infections [1953], p. 289

Vol. 3

KEY NO.

97 **COLITIS** (*cont.*):

Abstracts

New Heading **COLLAGEN DISEASES**

Article

98 **COLON—CARCINOMA OF**

Articles

Abstracts

Vol. 3

KEY NO.

109 DIVERTICULA OF THE ALIMENTARY TRACT

Abstracts

Diverticula of third part of duodenum [1951], p. 293
Sigmoido-cutaneous fistulae due to diverticulitis of the sigmoid colon [1951], p. 293
Diagnosis and treatment of acute diverticulitis of the caecum [1951], p. 294
Bleeding Meckel's diverticulum [1952], p. 234
Meckel's diverticulum: intussusception [1954], p. 261
Diverticulitis of the colon: surgical treatment [1955], p. 248
Symptoms and treatment of diverticulitis of the colon [1955], p. 249

110 DUCTUS ARTERIOSUS

No further references

111 EAR—AVIATION, SURGICAL ASPECTS OF

Abstract

Blast perforation of the ear-drum: aetiology and treatment [1951], p. 294

112 EAR—EXTERNAL EAR

Abstracts

Delayed onset of symptoms due to foreign bodies [1951], p. 295
Pathology and treatment of painful helicine nodules [1953], p. 290

113 EAR—INTERNAL EAR, ACUTE INFECTION

Abstracts

Sympathectomy and its influence on aural lesions [1952], p. 234
Pathology of vascular tumours [1953], p. 290
Postural vertigo due to sudden partial loss of vestibular function: aetiological considerations [1957], p. 318

114 EAR—INTERNAL EAR, CHRONIC INFECTION (NON-SUPPURATIVE)

Abstract

Preservation of the labyrinth [1952], p. 235

115 EAR—MALDEVELOPMENTS OF

Article

Surgical treatment of congenital atresia of the external auditory meatus [1957], p. 305

Abstracts

Deformities encountered in a microtic ear [1951], p. 295
Middle ear: malformations and related conditions [1952], p. 235
The auditory meatus in mongolism [1955], p. 249

Vol. 3

KEY NO.

104 CORNEA—DISEASES AND INJURIES (*cont.*):

Abstracts (cont.):

Corneal grafting [1959], p. 320
Contributions to technique [1959], p. 320
Preparation of corneal grafts: lyophilization [1959], p. 321
Lyophilized homografts and heterografts [1959], p. 321
Partial lamellar corneal grafts: survival of stromal cells [1959], p. 322
Donor-recipient sensitization [1959], p. 322
Corneal heterografts in rabbits [1959], p. 323
Interlamellar corneal homografts: immunity studies in rabbits [1959], p. 323
Use of preserved ocular tissues for transplantation [1959], p. 323
Viability of frozen corneas [1959], p. 324
Stored corneas: electrophoretic studies [1959], p. 324

105 DACTYLITIS

No further references

106 DEFORMITIES

Abstracts

Arthrogryposis: aetiology and treatment [1951], p. 291
Pectus excavatum: operative treatment [1951], p. 291
Madelung's deformity: treatment [1955], p. 248
Congenital dislocation of the hip [1955], p. 248

107 DERMOID AND EPIDERMOID CYSTS

No further references

108 DIABETES MELLITUS IN RELATION TO SURGERY

Articles

The management of lesions of the feet in diabetics [1957], p. 15
Necrotizing renal papillitis [1957], p. 265

Abstracts

Pregnancy in diabetic patients: foetal mortality [1951], p. 292
Treatment of diabetes: alcohol injection of splanchnic nerves [1951], p. 292
Charcot's joints in diabetic neuropathy [1952], p. 233
Neuropathic joints [1952], p. 234
Pre-operative insulin recommendation [1953], p. 289
Diabetes mellitus and pregnancy: perinatal deaths [1957], p. 235
Foetal aspects [1957], p. 236
Maternal aspects [1957], p. 236

Vol. 3

KEY NO.

121 EAR—OTOSCLEROSIS

Articles

The progress of microscopic aural surgery [1957], p. 298
Stapes mobilization [1957], p. 300

Abstracts

Haemostasis during fenestration operations [1951], p. 296
Some difficulties arising with fenestration operation [1952], p. 236
Treatment by Lempert's fenestration [1955], p. 250
Selection of patients for fenestration [1955], p. 250
Results of fenestration [1955], p. 250
Post-operative care and assessment of results of fenestration [1955], p. 251
Otosclerosis: technical problems in surgical treatment [1957], p. 316
Mobilization of the stapes [1957], p. 316
Results of operation [1957], p. 317

122 EFFUSIONS

No further references

123 ELECTRICAL REACTIONS OF MUSCLE AND NERVE

No further references

124 ELECTROCARDIOGRAPHY IN SURGICAL PROGNOSIS

No further references

New Heading ELECTRONICS

Article

The applications of electronics to clinical practice [1954], p. 67

125 ELEPHANTIASIS

Abstract

Post-operative lymph fistula: case reports [1956], p. 278

126 EMBOLISM—AIR, PATHOLOGY

No further references

127 EMBOLISM—FAT, PATHOLOGY

No further references

128 EMBOLISM—AIR AND FAT, CLINICAL ASPECT

Abstract

Relation between tissue injury and pulmonary fat embolism [1955], p. 251

129 EMPHYSEMA—SURGICAL

No further references

Vol. 3

KEY NO.

116 EAR—OTALGIA

No further references

117 EAR—OTITIS MEDIA, ACUTE MASTOIDITIS

Abstracts

The hypocellular mastoid: elucidation of its nature [1957], p. 314
Mastoid surgery: use of post-auricular flap [1959], p. 344
Radical mastoidectomy: technique for primary closure of wound [1959], p. 344

118 EAR—OTITIS MEDIA, CHRONIC CATARRHAL

Abstract

Eustachian deafness: response to nasopharyngeal irradiation [1957], p. 318

119 EAR—OTITIS MEDIA, CHRONIC SUPPURATIVE

Articles

Tympanoplasty [1957], p. 304
Plastic surgery of the sound-conducting mechanism [1959], p. 326
- Physiological principles [1959], p. 326
- Surgical principles [1959], p. 327
- Pre-operative investigations and treatment [1959], p. 329
- Types of operation [1959], p. 331
- Drainage of tympanic cavity [1959], p. 336
- Post-operative care [1959], p. 337
- Complications [1959], p. 338
- Results [1959], p. 339

Abstracts

Plastic surgery of sound-conducting apparatus: review of principles [1957], p. 315
Tympanoplastic operations: prognosis and results [1957], p. 316
Chronic otitis media: restoration of function of middle ear [1957], p. 317
Myringoplasty [1959], p. 342
Tympanoplasty [1959], p. 342
Basic techniques: recent advances [1959], p. 343
Result [1959], p. 344
Otological grafting: preserved autogenous skin [1959], p. 345
Management of deafness: scope of surgery [1959], p. 345
Chronic suppurative otitis media: plastic operations [1959], p. 346

120 EAR—OTITIS MEDIA, EXUDATIVE

No further references

Vol. 3

KEY NO.

139 EYE—CONGENITAL ABNORMALITIES: HEREDITY IN RELATION TO EYE DISEASE

Abstract

The clinical status of the contact lens [1951], p. 297

140 EYE—EXAMINATION OF, IN SURGICAL DIAGNOSIS

No further references

141 EYE—INJURIES: NON-INDUSTRIAL, INDUSTRIAL, WAR

No further references

142 EYE IN RELATION TO ENDOCRINE DISTURBANCE

Article

Malignant exophthalmos [1952], p. 60

Abstract

Malignant exophthalmos [1954], p. 261

143 EYE—THERAPEUTICS OF

Abstract

Treatment of eye emergencies [1956], p. 279

144 EYE—TROPICAL AND NUTRITIONAL DISEASE

No further references

145 EYE—TUBERCULOSIS

No further references

146 EYELIDS

No further references

Vol. 4

147 FACIAL PALSY

Abstracts

Traumatic palsy: indications and technique for surgical treatment [1951], p. 298
Traumatic palsy: management and surgical treatment [1953], p. 291
Idiopathic paralysis: symptoms [1953], p. 291
Facial-nerve decompression [1953], p. 291

Vol. 3

KEY NO.

130 ENDOMETRIOSIS

Article

Endometriosis [1957], p. 220

Abstract

Pathogenesis of endometriosis: implantation-induction theory [1956], p. 278

131 ENDOSCOPY—BRONCHOSCOPY

Article

Post-operative chest complications [1957], p. 99
Assisted removal of bronchial secretions [1957], p. 104

Abstracts

Diagnosis of foreign bodies [1951], p. 297
Foreign bodies in bronchi: incidence and treatment [1956], p. 279

132 ENDOSCOPY—CYSTOSCOPY

No further references

133 ENDOSCOPY—GASTROSCOPY

No further references

134 ENDOSCOPY—OESOPHAGOSCOPY

No further references

135 ENDOSCOPY—PERITONEOSCOPY

No further references

136 ENDOSCOPY—SIGMOIDOSCOPY

No further references

137 ENDOSCOPY—URETHROSCOPY

No further references

138 EPIPHYSES—DISEASES OF

Abstracts

Osteochondritis dissecans: aetiology [1955], p. 252
Familial incidence of osteochondritis dissecans [1955], p. 252
Legg-Perthes disease: two case reports [1957], p. 201
Epiphyseal stimulation: clinical evaluation [1957], p. 210
Growing epiphyseal cartilage and bone: autoradiographic study of organically bound carbon-14 [1957], p. 210
Homogeneous epiphyseal-cartilage grafts: experimental study [1957], p. 211

Vol. 4

KEY NO.

New Heading **FLUID AND ELECTROLYTE BALANCE**

Vol. 4

KEY NO.

148 FACIO-MAXILLARY INJURIES AND DEFORMITIES

Abstracts

Fractures of the maxillae: diagnosis and treatment [1951], p. 298
Dental aspects of treatment of clefts and perforations of the palate [1951], p. 299
Operative technique for cleft lip [1951], p. 299
Operative technique for cleft palate and hare-lip [1951], p. 300
Surgical treatment of hare-lip with double cleft and displaced pre-maxilla [1951], p. 300
Transparotid resection of lower jaw for tumours [1951], p. 301
Fractures of nasal pyramid [1954], p. 262
Complex fractures of middle third of face [1954], p. 263
Fracture of the zygoma: treatment [1955], p. 252

149 FALLOPIAN TUBES

Article

Ectopic gestation [1957], p. 226

Abstracts

Primary carcinoma: aetiology and treatment [1953], p. 292
Fallopian tubes: plastic operations [1957], p. 231

150 FASCIAL GRAFTS

Abstract

Suspension of the ptosed kidney by means of a fascia lata graft [1951], p. 301

151 FAT NECROSIS

No further references

152 FIBROSITIS

No further references

153 FILARIASIS

No further references

154 FISTULA IN ANO

Abstracts

Classification and treatment [1955], p. 253
Ano-rectal fistula: aetiology and surgical treatment [1956], p. 280

Vol. 4

KEY NO.

160 FROST-BITE

Abstracts

161 GALL-BLADDER AND BILE PASSAGES

Articles

Abstracts

Vol. 4

KEY NO.

157, 158, 159 FRACTURES, DISLOCATIONS, FRACTURE-DISLOCATIONS AND ALLIED INJURIES (*cont.*):

Abstracts (cont.):

Femoral neck: non-united and recent fractures [1954], p. 264
Wrist injury [1954], p. 265
Internal derangements of temporomandibular joint [1954], p. 265
Fractures of the scaphoid [1955], p. 254
Intracapsular fracture of the neck of the femur [1955], p. 255
Delayed union and non-union: pathogenesis and treatment [1955], p. 255
Condylar fractures of the knee joint [1955], p. 256
Patella: recurrent dislocation [1956], p. 280
Fractured calcaneus: treatment [1956], p. 280
Ankle: acute inversion sprains [1956], p. 281
Hip: recurrent dislocation [1956], p. 281
Shoulder: recurrent dislocation [1956], p. 281
Femoral neck: non-union after displaced intracapsular fractures [1956], p. 282
Displacement osteotomy of upper end of femur [1956], p. 282
Fractures of the odontoid process of the axis: clinical features [1957], p. 205
Fractures of the femoral neck: arterial supply to head of femur [1957], p. 206
Fractures of tibial condyle [1957], p. 206
Fractures of the lateral tibial condyle: treatment by skeletal traction and early mobilization [1957], p. 207
Healing of fractures in rats: studies with radioactive sulphur [1957], p. 212
Healing of fractures in dogs: influence of arteriovenous fistulas [1957], p. 212
Fracture patterns [1960], p. 127
Multiple fractures: systemic changes and early treatment [1960], p. 128
Open reduction of fractures [1960], p. 128
Supracondylar fractures of the humerus: varus deformity of elbow [1960], p. 129
Fractures of the forearm: internal fixation [1960], p. 130
Medullary fixation [1960], p. 130
Fractures of the carpal scaphoid: treatment with immobilization of the thumb [1960], p. 131
Fractures of the neck of the femur: early weight bearing [1960], p. 131
Undisplaced fractures of femoral neck in children: avascular necrosis [1960], p. 131
Intertrochanteric fractures of the femur: a 10-year analysis [1960], p. 132
Fracture of the intercondylar eminence of the tibia [1960], p. 132
Fractures of the shaft of the tibia [1960], p. 133
Supramalleolar fractures with associated subluxation [1960], p. 133
Comminuted fractures of the calcaneum: treatment by primary triple arthrodesis [1960], p. 134
Transchondral fractures of the talus [1960], p. 134
Familial joint laxity and recurrent dislocation of the patella: case history [1960], p. 147

Vol. 4

KEY NO.

167 GLAND-PUNCTURE AND ASPIRATION BIOPSY

Abstract

Tumour diagnosis: technique of trephine biopsy [1955], p. 262

168 GLANDERS

No further references

169 GLAUCOMA

Article

Glaucoma [1958], p. 348
- Physiology [1958], p. 348
- Classification [1958], p. 349
- Primary glaucoma [1958], p. 350
- Secondary glaucoma [1958], p. 358

Abstracts

Pathogenesis: aqueous veins [1951], p. 308
Surgical relief of glaucoma [1951], p. 308
Glaucoma associated with polycystic disease of the kidney [1952], p. 237
Glaucoma secondary to uveitis: cortisone treatment [1952], p. 238
Changes in ocular tension: dark-room tests [1958], p. 359
Applanation tonometry [1958], p. 359
Primary glaucoma: advanced chronic closed-angle glaucoma [1958], p. 360
Primary glaucoma: aetiology [1958], p. 360
Primary glaucoma: early diagnosis [1958], p. 361
Primary glaucoma: management [1958], p. 361

170 GLOMUS TUMOURS

Article

Tumours of the glomus jugulare or tympanic body [1954], p. 89

171 GLOTTIS—OEDEMA OF

No further references

172 GONORRHOEA

Abstract

Antibiotic treatment in the female [1952], p. 238

173 GOUT

No further references

Vol. 4

KEY NO.

161 GALL-BLADDER AND BILE PASSAGES (*cont.*):

Abstracts (cont.):

Report on a series of cholangiographic studies [1958], p. 127
Value and limitations of operative cholangiography [1958], p. 128
Carcinoid of the ampulla of Vater [1960], p. 101

162 GANGLION

No further references

163 GANGRENE, CLOSTRIDIAL (GAS GANGRENE)

No further references

164 GASTRO-COLIC FISTULA

Abstracts

Gastro-jejuno-colic fistula: a report on two cases [1951], p. 307
Gastro-jejuno-colic fistula: clinical picture and treatment [1956], p. 286

165 GASTROSTOMY

No further references

New Heading GENETICS

Article

Genetics and surgery [1960], p. 136
- Combined clinical and genetical separations of syndromes [1960], p. 136
- The pattern of inheritance of morphological abnormalities [1960], p. 137
- Chromosomal abnormalities in man [1960], p. 138
- Principles of estimating genetical risks [1960], p. 142

Abstracts

Chromosome aberration in human disease: a case of "polydyspondilism" [1960], p. 145
Human chromosomes in tissue culture [1960], p. 145
A sex-chromosome anomaly in Turner's syndrome: case report [1960], p. 145
Chromosomes in a patient with mongolism and Klinefelter's syndrome [1960], p. 146
A presumptive human xxy/xx mosaic [1960], p. 146
Familial joint laxity and recurrent dislocation of the patella: case history [1960], p. 147

166 GENITAL ORGANS—FEMALE EXTERNAL

Abstract

Vulva: carcinoma [1956], p. 286

Vol. 4

KEY NO.

178 HAND

Articles

Infections [1951], p. 231
The care of flexor tendon injuries in the hand [1959], p. 139
Division within the digital theca [1959], p. 139
Division in the palm and at wrist level [1959], p. 141
The operation of tendon grafting [1959], p. 142
Special problems [1959], p. 145
Causes of failure [1959], p. 147
Wringing machine injuries [1959], p. 383
Treatment [1959], p. 385

Abstracts

Reconstruction of the thumb: choice of method [1953], p. 296
Dupuytren's contracture: clinical features and treatment [1955], p. 263
Extensor tendons: treatment of recurrent dislocation [1955], p. 264
Minor injuries: standardized methods of treatment [1955], p. 264
Industrial injuries: management by the industrial surgeon [1955], p. 264
Major infections of the hand: diagnosis and treatment [1956], p. 287
Dupuytren's contracture: incidence, aetiology and predisposing causes [1956], p. 287
Reconstruction of amputated thumb [1959], p. 188
Septic-hand surgery: dispensability of post-operative penicillin [1959], p. 390
Dupuytren's contracture [1960], p. 18
Herpes simplex: herpetic whitlow [1960], p. 382

179 HEART AND PERICARDIUM

Articles

Chronic constrictive pericarditis [1953], p. 87
Surgery of cardiac septal defects [1958], p. 178
Atrial septal defect [1958], p. 178
Ventricular septal defect [1958], p. 185
Profound hypothermia in cardiac surgery [1960], p. 148
The apparatus [1960], p. 149
Method of use [1960], p. 150
The immediate results [1960], p. 155
Comparison between profound hypothermia and cardio-pulmonary by-pass [1960], p. 155
Future development [1960], p. 156

Abstracts

Post-operative changes in output [1952], p. 239
Chronic constrictive pericarditis: diagnosis and treatment [1955], p. 265
Aortic valve surgery: simultaneous pressure measurements [1958], p. 193
Aortic stenosis: surgical treatment [1958], p. 193
Mitral insufficiency: encircling suture in surgical treatment [1958], p. 194
Aortic valve prosthesis: experimental study [1958], p. 194

Vol. 4

KEY NO.

Vol. 4

KEY NO.

183 HETEROTOPIA

No further references

184 HICCUP

No further references

Vol. 5

185 HODGKIN'S DISEASE, OTHER RETICULOSES, RETICULO-SARCOMA AND MYELOMATOSIS

Abstract

Hodgkin's disease [1954], p. 267

186 HORMONES

Articles

Post-menopausal bleeding [1957], p. 221
Endocrine aspects of gynaecology [1959], p. 191
- Normal fluctuations in sex hormone secretion [1959], p. 191
- Oestrogen preparations [1959], p. 192
- Progestational steroids [1959], p. 194
- The endocrine control of normal and abnormal uterine bleeding [1959], p. 200
- Management of functional uterine haemorrhage [1959], p. 202
- Treatment of dysmenorrhoea [1959], p. 205
- Amenorrhoea [1959], p. 206
- Progestins during pregnancy [1959], p. 206

Abstracts

Hypothyroidism [1954], p. 267
Biochemical contributions to urology: synthetic oestrogens and aldosterone [1957], p. 295

187 HYDATID DISEASE

Abstract

Operative removal of univesicular pulmonary hydatid cyst [1951], p. 314

188 HYPERHIDROSIS AND ALLIED STATES

No further references

189 HYPERPIESIA

No further references

Vol. 4

KEY NO.

179 HEART AND PERICARDIUM (*cont.*):

Abstracts (cont.):

Coronary artery disease: auxiliary myocardial vascularization by prosthetic graft implantation [1958], p. 195
Coronary artery disease: myocardial vascularization by implantation of left common carotid artery [1958], p. 195
Coronary artery curettement: experiments on dogs [1958], p. 196
Surgical treatment of mitral stenosis: transventricular approach with mechanical dilator [1960], p. 158
Pulmonary stenosis: valvotomy [1960], p. 158
Atrial septal defect, secundum: open surgical repair [1960], p. 159
Anomalous pulmonary venous drainage [1960], p. 160
Simultaneous repair of mitral and tricuspid valves [1960] p. 160
Surgical treatment of aortic insufficiency: chronic experimental studies [1960], p. 161
Closure of cardiac defects: use of atrial grafts [1960], p. 161
Antiheparin potency of polybrene and protamine: patients undergoing extracorporeal circulation [1960], p. 162
Post-stenotic dilation: experimental observations [1960], p. 258

180 HERNIA

Article

Recurrent hernia [1951], p. 146

Abstracts

Recurrent inguinal hernia: skin-grafting at operation [1952], p. 240
Oesophageal hiatus hernia: operative procedure [1953], p. 297
Intersigmoid hernia [1954], p. 266
Complications: incarceration of a double loop [1955], p. 265
Perineal hernia causing acute intestinal obstruction [1955], p. 266
Treatment: results in 867 primary indirect inguinal hernioplasties [1955], p. 266
Inguinal herniorrhaphy: criticism of procedures [1956], p. 288
Problems in the treatment of hernia [1956], p. 288
Retromesocolic hernia [1956], p. 289

181 HERNIA—DIAPHRAGMATIC

Abstracts

Traumatic hernias of the diaphragm [1951], p. 313
Differential diagnosis from coronary artery disease [1951], p. 314
Surgical anatomy: the crura of the diaphragm [1955], p. 266

182 HERPES ZOSTER

Abstract

Herpes zoster: involvement of urinary bladder [1960], p. 381

Vol. 5

KEY NO.

195-199 **INTESTINES** (*cont.*):

Abstracts

Multiple argentaffinomas of the ileum [1952], p. 240
Argentaffinoma of ileum with perforation [1952], p. 240
Congenital duodenal obstruction and mongolism [1952], p. 241
Congenital duplication of the small intestine [1952], p. 241
Technique of surgery of the colon [1955], p. 267
Duodenal obstruction due to annular pancreas [1955], p. 268
Ileostomy dysfunction: mechanism and prevention [1955], p. 268
Regional ileitis: history and morbid anatomy [1955], p. 269
Acute post-operative enteritis: severe intestinal bleeding supervening [1955], p. 269
Congenital obstruction of the small intestine: surgical treatment [1955], p. 270
Benign tumours of the small intestine [1956], p. 289
Malignant argentaffinoma of the small intestine [1956], p. 290
Primary mesenteric venous thrombosis: symptoms and treatment [1956], p. 290
Congenital atresia below the duodenum: operative mortality [1956], p. 291
Obstruction of colon: treatment [1957], p. 75
Ileocystostomy for neurogenic bladder [1958], p. 263
Ileocystoplasty for bladder contracture [1958], p. 264
Total replacement of ureter [1958], p. 264
Ureteral substitution by isolated ileal loop [1958], p. 265
Crohn's disease: evaluation of current management [1958], p. 128
Crohn's disease: indications for surgical intervention [1958], p. 129
Acute small bowel obstruction: treatment [1960], p. 103
Physiological response of the small bowel to ischaemia: animal experimentation [1960], p. 255

200 **INTUSSUSCEPTION**

Abstracts

Adult incidence: aetiology and symptomatology [1955], p. 270
Recurrent ileocolic intussusception associated with hypertrophy of Peyer's patches [1956], p. 291

201 **ISCHAEMIA**

Abstract

Physiological response of the small bowel to ischaemia: animal experimentation [1960], p. 255

202 **JAUNDICE**

Abstracts

Intrahepatic obstructive jaundice of unknown aetiology [1952], p. 241
Surgical treatment: value of operative cholangiography [1955], p. 271
Obstructive jaundice: clinical diagnosis [1956], p. 291
Diagnostic procedures in obstructive jaundice [1956], p. 292
Decompression of hepatic duct system [1956], p 292
Virus hepatitis: intrahepatic bile stasis [1960], 380

Vol. 5

KEY NO.

190 IMMERSION-FOOT

No further references

191 IMPOTENCE

No further references

192 INFECTION, INFECTIONS AND INFLAMMATION

Articles

The general pathology of repair [1955], p. 192
Use of antiseptics in labour [1957], p. 228

Abstract

Cortisone: use in suppressing inflammatory reactions [1956], p. 289

193 INJURY—CIVIL AND INDUSTRIAL

Abstract

Road accidents: analysis of type of injury and vehicle in 717 cases [1955], p. 267

194 INJURY—COMPRESSION

No further references

195-199 INTESTINES

Article

Intestines [1952], p. 171
Necrotizing enteritis [1955], p. 104 [1958], p. 60
Cytology in the diagnosis of cancer of the alimentary tract [1957], p. 66
Acute necrotizing enterocolitis [1957], p. 61
Fluid and electrolyte disturbances [1958], p. 47
- Necrotizing enteritis [1958], p. 60
- Anatomical considerations [1958], p. 236
- Physiological considerations [1958], p. 237
- Preparation of the ileal loop [1958], p. 238
- Ileocystoplasty and uretero-ileocystoplasty [1958], p. 239
- Ileum used as a conduit to the exterior [1958], p. 257
- Use of a loop of ileum in revision procedures [1958], p. 259
- Summary [1958], p. 262

Crohn's disease [1958], p. 84
- Pathology [1958], p. 84
- Experimental work [1958], p. 85
- Causation [1958], p. 86
- Clinical features and diagnosis [1958], p. 88
- Radiological examination [1958], p. 93
- Management [1958], p. 93
- Treatment of recurrence after operation [1958], p. 98

Vol. 5

KEY NO.

210 KIDNEY AND URETER—GROWTHS

Abstracts

Haemangioma: clinical picture [1952], p. 243
Thrombosis of vena cava associated with renal neoplasia [1952], p. 244
Retrocaval displacement [1952], p. 244
Transthoracic nephrectomy [1952], p. 244
Malignant tumours: symptoms, diagnosis and treatment [1953], p. 297
Late metastasis from renal carcinoma [1953], p. 297
Haemangioma of kidney [1954], p. 268
Neuroblastoma of kidney [1954], p. 269
Perinephric cysts [1954], p. 269
Renal hypoplasia [1954], p. 269
Disease of the ureteric remnant following nephrectomy [1955], p. 273
Kidney tumours: radiological diagnosis [1957], p. 282
Hypernephroma: associated with polycythaemia [1960], p. 365

211 KIDNEY AND URETER—HYDRONEPHROSIS AND PYONEPHROSIS

Article

Hydronephrosis [1957], p. 265
 Intermittent hydronephrosis [1957], p. 266
 Intubation [1957], p. 266

Abstracts

Transparietal puncture of the renal pelvis [1951], p. 317
Plastic repair of retrocaval ureter [1951], p. 317
Congenital hydronephrosis due to ureteropelvic obstruction [1955], p. 274

New Heading KIDNEY AND URETER—NEPHRECTOMY

Article

Partial nephrectomy [1956], p. 189
 Indications [1956], p. 189
 General principles in the operation of partial nephrectomy [1956], p. 212
 Complications after partial nephrectomy [1956], p. 222

Abstracts

Partial nephrectomy: a critical study [1960], p. 184
Observations on 211 cases [1960], p. 184

212 KIDNEY AND URETER—STONE

Article

Progress in genito-urinary surgery [1957], p. 262
 Urinary lithiasis [1957], p. 269
 Science and clinical urology [1957], p. 279

Abstracts

Non-opaque urinary calculus [1954], p. 270
Impacted ureteric calculus: treatment [1955], p. 274
Mechanism of renal calculus formation [1955], p. 274
Anuria: complication of retrograde pyelography [1955], p. 275

Vol. 5

KEY NO.

203 JOINTS—ARTHROGRAPHY

No further references

204 JOINTS—CAISSON DISEASE OF

No further references

205 JOINTS—INJURIES AND ACUTE INFECTIONS

Abstracts

Temporomandibular arthrosis: traumatic causation [1955], p. 271
Wear and tear in joints: experimental findings [1957], p. 211

206 JOINTS—INTERNAL DERANGEMENTS OF THE KNEE

No further references

207 JOINTS—TUBERCULOSIS

Article

Bone and joint tuberculosis: the value of antibiotics [1954], p. 42

Abstracts

Streptomycin in surgery [1952], p. 242
Treatment by chemotherapy [1955], p. 272
Use of anti-tubercular drugs in joint tuberculosis [1956], p. 293

208 KIDNEY AND URETER—CYSTS

Article

Hydro-ureter [1955], p. 93

Abstracts

Polycystic disease: radical operation [1952], p. 242
Multilocular cysts [1952], p. 242
Renal cysts in the newborn [1955], p. 272
Mega-ureter with vesico-ureteric reflux [1955], p. 273
Megaloureter: examination, pathology and treatment [1957], p. 285
Investigation and management [1957], p. 285

209 KIDNEY AND URETER—DENERVATION OF THE KIDNEY

Abstract

Nephroptosis: nephropexy [1956], p. 293

Vol. 5

KEY NO.

213 KIDNEY AND URETER—TUBERCULOSIS (*cont.*):

Abstracts (cont.):

Indications for partial resection [1957], p. 284
Frequency: diagnosis and treatment [1957], p. 284
Partial nephrectomy: a critical study [1960], p. 184
Observations on 211 cases [1960], p. 184

214 LACRIMAL APPARATUS—INJURIES AND DISEASES

Abstracts

Primary adenocarcinoma of the lacrimal gland [1952], p. 245
Mixed tumour of lacrimal gland [1952], p. 245

215 LARYNX—DIRECT LARYNGOSCOPY AND ASPIRATION TREATMENT IN LARYNGEAL DIPHTHERIA

No further references

216 LARYNX—SURGICAL DISEASES OF

Articles

Speech after laryngectomy [1954], p. 105
Paralysis of the larynx [1956], p. 224
Carcinoma of the larynx [1957], p. 310
    Radiotherapy [1957], p. 310
Post-cricoid carcinoma [1957], p. 311
    Treatment [1957], p. 311

Abstracts

Streptomycin in the treatment of scleroma [1951], p. 318
Indications for a preliminary tracheotomy [1951], p. 318
Surgery after failure of radiotherapy for carcinoma [1952], p. 245
Emergency operations for the treatment of grave dyspnoea [1952], p. 246
Malignant disease: treatment by radiotherapy [1953], p. 298
Laryngeal mechanism: cine-radiographic studies during swallowing [1957], p. 319
Carcinoma of the larynx: surgical treatment [1957], p. 320
Carcinoma of the larynx and hypopharynx: radical *en bloc* operation [1957], p. 321

217 LAW IN RELATION TO SURGERY

Article

Developments in the law in relation to surgery [1955], p. 176
    Consent to operations and criminal liability [1955], p. 176
    The liability of hospitals for negligence [1955], p. 177
    Limitation of actions [1955], p. 180

Vol. 5

KEY NO.

212 KIDNEY AND URETER—STONE (*cont.*):

Abstracts (cont.):

Modification of urinary surface tension [1955], p. 275
Ion-binding properties of electrophoretically homogeneous muco-proteins of urine [1955], p. 276
Mechanism of the formation and control of calculus disease by the kidney [1955], p. 276
Renal calcinosis: case reports, aetiology [1957], p. 281
Two case reports [1957], p. 282

New Heading KIDNEY AND URETER—SURGICAL ASPECTS

Articles

Progress in genito-urinary surgery [1957], p. 262
Use of the ileum in urological procedures [1958], p. 236
  Isolated segment of ileum used to replace the ureter [1958], p. 254

Abstracts

Injuries of lower ureter: treatment [1957], p. 286
Ureteral substitution by isolated ileal loop [1958], p. 265
"Cup-patch" technique of ileocystoplasty: bladder enlargement or partial substitution [1960], p. 185

213 KIDNEY AND URETER—TUBERCULOSIS

Articles

Genito-urinary tuberculosis [1957], p. 268
  Chemotherapy [1957], p. 268
Urinary tuberculosis [1960], p. 164
  General principles of modern therapy [1960], p. 165
  Antituberculous drugs [1960], p. 166
  Ambulatory treatment [1960], p. 166
  Urine examinations [1960], p. 167
  Institutional versus ambulatory treatment [1960], p. 167
  Indications for surgery [1960], p. 168
  The calyx [1960], p. 168
  The pelvi-ureteric junction [1960], p. 174
  Lower ureteric obstruction [1960], p. 174
  The systolic bladder [1960], p. 179
  Urinary diversion [1960], p. 183

Abstracts

Obstruction of the ureter and its pelvis due to tuberculosis [1955], p. 277
Investigation of conservative methods of treatment [1956], p. 294
Selective principle in treatment of urogenital tuberculosis [1956], p. 294
Chemotherapy in treatment of renal tuberculosis [1956], p. 295
Treatment with different preparations of PAS [1956], p. 295
Tuberculosis of the genito-urinary tract: drug therapy [1957], p. 283
Pathological anatomy and histopathology following chemotherapy [1957], p. 283

Vol. 5

KEY NO.

213 KIDNEY AND URETER—TUBERCULOSIS (*cont.*):

Abstracts (cont.):

Indications for partial resection [1957], p. 284
Frequency: diagnosis and treatment [1957], p. 284
Partial nephrectomy: a critical study [1960], p. 184
Observations on 211 cases [1960], p. 184

214 LACRIMAL APPARATUS—INJURIES AND DISEASES

Abstracts

Primary adenocarcinoma of the lacrimal gland [1952], p. 245
Mixed tumour of lacrimal gland [1952], p. 245

215 LARYNX—DIRECT LARYNGOSCOPY AND ASPIRATION TREATMENT IN LARYNGEAL DIPHTHERIA

No further references

216 LARYNX—SURGICAL DISEASES OF

Articles

Speech after laryngectomy [1954], p. 105
Paralysis of the larynx [1956], p. 224
Carcinoma of the larynx [1957], p. 310
    Radiotherapy [1957], p. 310
Post-cricoid carcinoma [1957], p. 311
    Treatment [1957], p. 311

Abstracts

Streptomycin in the treatment of scleroma [1951], p. 318
Indications for a preliminary tracheotomy [1951], p. 318
Surgery after failure of radiotherapy for carcinoma [1952], p. 245
Emergency operations for the treatment of grave dyspnoea [1952], p. 246
Malignant disease: treatment by radiotherapy [1953], p. 298
Laryngeal mechanism: cine-radiographic studies during swallowing [1957], p. 319
Carcinoma of the larynx: surgical treatment [1957], p. 320
Carcinoma of the larynx and hypopharynx: radical *en bloc* operation [1957], p. 321

217 LAW IN RELATION TO SURGERY

Article

Developments in the law in relation to surgery [1955], p. 176
    Consent to operations and criminal liability [1955], p. 176
    The liability of hospitals for negligence [1955], p. 177
    Limitation of actions [1955], p. 180

Vol. 5

KEY NO.

218 LENS—DISEASES AND INJURIES

Abstract

Cataract: intra-ocular acrylic lenses in post-operative management [1952], p. 246

219 LEPROSY

Article

Hand reconstruction in leprosy [1954], p. 117

220 LIGATURES AND SUTURES

No further references

221 LIMBS—ABSENCE OF

No further references

222 LIPOID METABOLISM AND LIPOID GRANULOMA

No further references

223 LIVER—CIRRHOSIS

Articles

Portal hypertension [1953], p. 202
Portal hypertension [1957], p. 123
- Management of acute haemorrhage [1957], p. 123
- Interval surgery [1957], p. 123
- Hepatic coma [1957], p. 125
- Blood changes and ascites [1957], p. 126

Abstracts

Venography: experimental study of hepatic veins [1952], p. 246
Chronic hepatitis with portal hypertension: effect of venous shunt [1952], p. 247
Portal hypertension treated by ligation of hepatic and splenic arteries [1952], p. 247
Portal hypertension: treatment by porta-caval anastomosis [1953], p. 298
Portal hypertension: treatment according to type of obstruction [1955], p. 277
Portal hypertension associated with massive gastro-intestinal bleeding: experimental and clinical findings [1957], p. 80
Portal hypertension: treatment by hepatic artery ligation [1957], p. 131
Classification and surgical treatment in infancy and childhood [1957], p. 132
The complexity of liver disease: hepatic circulation, portal hypertension, ascites and ammonia metabolism [1957], p. 132
Hepatic coma: treatment and prognosis [1957], p. 133

Vol. 5

KEY NO.

New Heading **LIVER—SURGERY**

Article

Survey on partial hepatectomy with especial reference to liver anatomy [1959], p. 40
Anatomical considerations [1959], p. 40
Partial hepatectomy [1959], p. 47

224 LUMBAR PUNCTURE

No further references

New Heading **LUNG—SURGERY**

Article

Progress in pulmonary surgery [1958], p. 152
Pulmonary suppuration [1958], p. 152
Empyema [1958], p. 156
Bronchiectasis [1958], p. 160

Abstracts

Large air cysts of the lung: diagnosis and surgical treatment [1958], p. 172
Bronchial adenoma [1958], p. 172
Carcinoma of the lung: diagnosis by biopsy and cytological smears [1958], p. 173
Carcinoma of the lung: involvement of the thoracic wall [1958], p. 173
Carcinoma of the lung: results of raising the resectability rate [1958], p. 174
Pulmonary tuberculosis: results of thoracoplasty [1958], p. 174
Pulmonary tuberculosis: results of lung resection [1958], p. 175
Thoracic actinomycosis [1958], p. 175
Ventilatory insufficiency: treatment by tracheostomy and artificial ventilation [1958], p. 176

225 LUNG—TUMOURS

Articles

Carcinoma of the bronchus [1957], p. 88
Delay in submission for operation [1957], p. 89
Direction of surgical endeavour [1957], p. 89
Radical pneumonectomy [1957], p. 89
Lobectomy [1957], p. 90
The uses of prostheses after pneumonectomy [1957], p. 90
Sleeve resection of the bronchus [1957], p. 91
Management of the inoperable patient [1957], p. 91
Pulmonary cysts [1957], p. 92
Epithelial cysts [1957], p. 93
Emphysematous cysts [1957], p. 94
Emphysematous cysts in infancy [1957], p. 98
Tracheostomy [1957], p. 98

Vol. 5

KEY NO.

225 LUNG—TUMOURS (*cont.*):

Abstracts

Cardiovascular disturbances in bronchial carcinoma [1951], p. 319
Diagnosis of cancer of the lung [1951], p. 319
Incidence of metastasis of lung tumours of the brain [1951], p. 320
Carcinoma of the lung: incidence [1952], p. 247
Coexistence of pulmonary tuberculosis with bronchial carcinoma [19
p. 248
Morbid anatomy of cancer of the lung [1953], p. 298
Cytology of sputum [1956], p. 295
Asymptomatic cancer: surgical treatment [1956], p. 296
Relation of occupation and smoking to lung cancer [1956], p. 296
Carcinoma of the bronchus: mode of spread [1957], p. 109
The case for lobectomy [1957], p. 110
Results of radiotherapy [1957], p. 111

226 LUPUS VULGARIS

Abstracts

Intralesional calciferol treatment [1952], p. 248
Lupus erythematosus: morbid anatomy [1953], p. 299

227 LYMPHOGRANULOMA INGUINALE

No further references

Vol. 6

228 MALINGERING

No further references

229 MANIPULATIVE SURGERY

No further references

230 MEDIASTINUM

Abstract

Mediastinal fascia: anatomy and applied anatomy [1953], p. 299

231 MELAENA AND BLOOD IN THE STOOLS

Abstract

Occult blood in faeces [1954], p. 270

232 MELANOMA

Article

Melanomas and their spread [1956], p. 236

Abstract

Treatment of malignant melanoma [1953], p. 300

Vol. 6

KEY NO.

233 MENINGES—MENINGITIS, ACUTE AND CHRONIC

Article

Surgical aspects of meningitis [1953], p. 136

Abstracts

Surgical aspects of meningitis [1951], p. 320
Neurosurgery in diagnosis and treatment of tuberculous meningitis [1952], p. 249
Congenital dermal sinus associated with meningitis [1952], p. 249

234 MOUTH AND PHARYNX—MALIGNANT DISEASE OF

Articles

Maxilla—carcinoma of [1956], p. 33
Cytology in the diagnosis of cancer of the alimentary tract [1957], p. 66
The oral cavity [1957], p. 67

Abstracts

Massive roentgen therapy in inoperable oral cancer [1952], p. 250
Combined radiotherapy and surgery [1952], p. 250
Carcinoma of the hypopharynx [1953], p. 300
Malignant tumours and their treatment [1953], p. 301
Biopsy studies of cancer of the gums [1953], p. 301
Epithelioma of the chin [1954], p. 271
Carcinoma of floor of mouth [1954], p. 271
Malignant disease of the upper jaw: treatment [1955], p. 277
Chondrosarcoma of the maxilla: treatment [1955], p. 278
Evolution of major surgery: relation between radiotherapy and surgery [1956], p. 297
Carcinoma of the hypopharynx: laryngo-oesophagectomy with laryngo-tracheal autograft [1957], p. 321

235 MUSCLE AND TENDON—DISEASES AND INJURIES

Article

Diseases of muscle [1959], p. 149
Muscular dystrophy [1959], p. 149
Myositis [1959], p. 151
Amyotonia congenita [1959], p. 153
Myasthenia gravis [1959], p. 153

Abstracts

The latissimus dorsi as a replacing muscle [1951], p. 321
Herniated intervertebral disc [1954], p. 273
Localized myositis ossificans: pathogenesis [1955], p. 278
Malignant tumours of skeletal muscle: research into histogenesis [1956], p. 297
Pigmented villo-nodular tenosynovitis [1956], p. 297
Thoracic outlet syndrome: treatment [1957], p. 200
Flexor tenodesis: provision of automatic grasp [1957], p. 203
Iliopsoas transfer for hip instability: a follow-up study [1960], p. 18

Vol. 6

KEY NO.

236 *NECK—CELLULITIS*

No further references

237 NECK—CUT THROAT

Abstract

Fracture of the hyoid bone [1951], p. 321

238 NECK—CYSTIC SWELLINGS OF

Abstracts

Causation and treatment of branchial cysts [1951], p. 321
Branchial cysts: surgical treatment [1956], p. 298

239 NECK—TUBERCULOUS GLANDS

Abstract

Pathology and treatment of cervical or mesenteric lymphadenitis [1952], p. 250

240 NEOPLASMS—INNOCENT AND MALIGNANT

Abstracts

Modern methods of treating malignant disease [1951], p. 322
Latent carcinoma [1955], p. 279
Carcinoma of the mastoid cavity [1955], p. 279
Malignant synovioma: report on treatment of 3 cases [1955], p. 280
Dermoid tumours: difficulties in diagnosis [1956], p. 298
Multiple neurofibromatosis: disease groups and associated lesions [1956], p. 299

241 NERVES—CRANIAL

Articles

Neurofibromas of the fifth cranial nerve [1958], p. 340
Gliomas of the optic pathways in childhood [1958], p. 341

242 NERVES, *PERIPHERAL—INJURIES*

Abstracts

Ischaemic lateral popliteal nerve palsy: vascular disturbances associated with foot-drop [1955], p. 280
Two-stage operation involving minimal traction injury [1956], p. 299

243 NEURALGIA—TRIGEMINAL, GLOSSOPHARYNGEAL

Abstracts

Technique of alcohol injection of Gasserian ganglion [1951], p. 323
Review of treatment of trigeminal neuralgia [1952], p. 251
Facial neuralgias [1960], p. 291

Vol. 6

KEY NO.

244 NOSE, NASOPHARYNX AND ACCESSORY SINUSES

Abstracts

Diagnosis and treatment of mucocele of the sinuses [1951], p. 324
Malignant tumours of the nasopharynx [1952], p. 251
Treatment of ulcerative destruction of the nose with chloramphenicol [1953], p. 301
Chondrosarcoma: clinical picture and prognosis [1953], p. 302
Intranasal encephaloceles: diagnosis and treatment [1953], p. 302
Carcinoma of the nose: surgical treatment [1955], p. 280
Frontal sinusitis: review of treatment by external surgery [1955], p. 281
Maxillary sinusitis: treatment [1956], p. 300

New Heading OBSTETRICS

Abstracts

Placenta: anatomy of the villus [1957], p. 233
Anatomy of cotyledons [1957], p. 233
Pre-eclampsia and eclampsia: aetiology [1957], p. 234
Toxaemia of pregnancy: ABO blood groups [1957], p. 234
Antigen-antibody reaction [1957], p. 235
Rh-sensitized patient: management [1957], p. 236
Intravenous pitocin: use in obstetrics [1957], p. 237
Transvaginal pudendal nerve block: improved approach [1957], p. 238
Diagnosis of foetal sex: analysis of amniotic fluid cells [1957], p. 238
Pulmonary hyaline membrane syndrome: pathogenesis [1957], p. 239
Inevitable miscarriage: suture of the cervix uteri [1958], p. 226
Post-partum oxytocics: clinical evaluation [1958], p. 226
Effective uterine blood flow during labour [1958], p. 227
Local analgesia and Kielland's forceps [1958], p. 227
Traumatic maternal birth palsy [1958], p. 228
Mitral valvotomy during pregnancy [1958], p. 228

245 ODONTOMES AND EPITHELIAL CYSTS

Abstracts

Diagnosis and treatment of maxillary cysts [1951], p. 324
Epithelial cysts of the jaws: adamantinoma [1956], p. 300
Multiple dental cysts [1956], p. 300

246 OEDEMA—TRAUMATIC

No further references

247 OESOPHAGUS

Articles

Reconstruction of the trachea, hypopharynx and cervical oesophagus [1951], p. 193
Cardiospasm [1953], p. 178
Carcinoma of the oesophagus [1954], p. 210

Vol. 6

KEY NO.

247 OESOPHAGUS (*cont.*):

Articles (cont.):

Abstracts

Vol. 6

KEY NO.

248 OMENTUM

Abstracts

Diagnosis and treatment of torsion of the omentum [1951], p. 326
Torsion of great omentum: surgical treatment [1952], p. 254

249 OPTIC NERVE

No further references

250 ORBIT—INJURIES, INFECTIONS, NEOPLASMS

Abstract

Tumours of the orbit [1951], p. 327

New Heading ORGAN TRANSPLANTATION

Articles

Organ transplantation [1955], p. 204
Progress in genito-urinary surgery [1957], p. 262
- The kidney [1957], p. 263

Recent advances in bone marrow transplantation [1960], p. 186
- The preparation and manipulation of haemopoietic cells for transfusion [1960], p. 186
- Clinical applications [1960], p. 187
- Future applications [1960], p. 190

Homografts and the complexities of chimaeras [1960], p. 197
- Immune response [1960], p. 197
- Immunological tolerance [1960], p. 200
- Reduction or abolition of immunological reactivity [1960], p. 201
- Sulzberger-Chase phenomenon [1960], p. 203
- The radiation chimaera [1960], p. 204

Tissue transplantation [1960], p. 224
- The genetic laws of transplantation [1960], p. 225
- The immunological basis of the transplantation rejection process [1960], p. 226
- Modifications of the homotransplant rejection phenomenon [1960], p. 228
- Foetal grafts [1960], p. 232
- Auto-immune disease [1960], p. 232
- Natural history of homotransplanted tissues [1960], p. 234
- Homotransplantation of skin [1960], p. 234
- Transplantation of kidney [1960], p. 236
- Bone marrow transplantation [1960], p. 243
- Transplantation of endocrine tissue and Halsted's law [1960], p. 247

Abstracts

Whole-body irradiation and marrow transplantation [1960], p. 191
Transfusion and grafts of homologous bone marrow: accidental irradiation of human beings [1960], p. 192

Vol. 6

KEY NO.

New Heading **ORGAN TRANSPLANTATION** *(cont.)*:

Abstracts (cont.):

251 **ORTHODONTICS**

Article

Vol. 6

KEY NO.

251 **ORTHODONTICS** (*cont.*):

Abstracts

Trends in orthodontic treatment [1951], p. 327
Mandibular condyle: development, growth and pathology [1960], p. 28
Pain in temporomandibular arthroses: distribution and treatment [1960], p. 289
Costen's syndrome [1960], p. 290
Dental diagnosis of pain: temporomandibular joint and myofascial tigge areas [1960], p. 291
Occlusal rehabilitation [1960], p. 292

252 **ORTHODONTICS—SURGERY OF**

No further references

253 **ORTHOPTIC TRAINING**

No further references

254 **OVARY**

Article

Recent advances in gynaecology and obstetrics [1957], p. 215
Ovarian carcinoma [1957], p. 220
Clinical aspects of non-ovulation [1957], p. 222
Clinical features of non-ovular menstruation [1957], p. 222
Diagnosis of non-ovulation [1957], p. 223
Presenting symptom in non-ovulation [1957], p. 224
Types of non-ovular menstruation [1957], p. 224
Primary dysmenorrhoea [1957], p. 227

Abstracts

Carcinoma: review of a series [1952], p. 254
Carcinoma: vaginal metastases [1953], p. 303
Ovarian tumours: post-operative irradiation [1956], p. 302
Prognosis of primary ovarian cancer [1956], p. 302
Rhabdomyosarcoma of the ovary [1956], p. 302
Menstruation: irregular shedding of the endometrium [1957], p. 232
Ovarian cancer: routine intracavitary administration of colloidal ^{198}Au [1959], p. 377

255 **OXYGEN THERAPY**

No further references

256 **PAIN—CAUSALGIA**

No further references

Vol. 6

KEY NO.

257 PANCREAS

Articles

Abstracts

Vol. 6

KEY NO.

257 PANCREAS (*cont.*):

Abstracts (cont.):

Acute pancreatitis: natural history [1957], p. 79
Chronic relapsing pancreatitis: radical resection of pancreas [1957], p. 79
Pancreatic disease: diagnosis [1959], p. 73
Chronic relapsing pancreatitis: retrograde surgical drainage of pancreas [1959], p. 74
Sphincteroplasty for recurrent pancreatitis [1959], p. 74
Pancreatic pseudocyst: clinical and surgical aspects [1959], p. 75
Acute pancreatitis with peritoneal fat necrosis: radiological diagnosis [1959], p. 75
Pancreatoduodenal resection [1959], p. 76
Hyperparathyroidism and acute pancreatitis [1959], p. 76
Carcinoid of the ampulla of Vater [1960], p. 101
Pancreatic surgery [1960], p. 310
Relation of pancreatic ducts to the islets of Langerhans [1960], p. 311
Pancreatic islet-cell hyperplasia: malabsorption and jejunal ulceration due to gastric hypersecretion [1960], p. 311
Spontaneous hyperinsulinism [1960], p. 311
Hyperinsulinism: diabetogenic effect [1960], p. 312
Islet cell tumours of the pancreas [1960], p. 312
Organic hyperinsulinism: insulin sensitivity [1960], p. 313
Idiopathic infantile hypoglycaemia [1960], p. 313
Hypoglycaemia due to non-pancreatic mesodermal tumours: case reports [1960], p. 314

258 PARALYSIS—MANAGEMENT OF

Abstracts

Transplantation of the spinal cord in paraplegia [1951], p. 328
Infantile hemiplegia treated by hemispherectomy [1952], p. 255
Hemiplegia: treatment [1955], p. 286

259 PARATHYROID GLAND—DISEASES

Articles

Parathyroids [1957], p. 154
  Hypoparathyroidism [1957], p. 154
  Hyperparathyroidism [1957], p. 154
The parathyroid glands [1959], p. 129

Abstracts

Hyperparathyroidism: results of surgical treatment [1951], p. 329
Hyperparathyroidism: differential diagnosis from sarcoidosis [1952], p. 256
Hyperparathyroidism [1957], p. 175

260 PELLAGRA

No further references

Vol. 6

KEY NO.

261 PELVIC ORGANS—DISPLACEMENT

Article

Stress incontinence [1951], p. 259

Abstracts

Stress incontinence in women with genital prolapse [1952], p. 256
Stress incontinence: failure of cure following vaginal operative procedure [1952], p. 256

New Heading PELVIC ORGANS—VISCERECTOMY

Article

Pelvic organs—viscerectomy [1954], p. 131

262 PEPTIC ULCER AND ITS COMPLICATIONS

Articles

Gastric ulcer: the vascular anatomy of the human stomach in relation to [1952], p. 104
Peptic ulcer of the stomach and duodenum [1959], p. 15
- Aetiology [1959], p. 15
- Pathogenesis [1959], p. 16
- Some pathological considerations [1959], p. 29
- Diagnosis [1959], p. 30
- Medical management [1959], p. 30
- Surgical management [1959], p. 31

Abstracts

Causation of peptic ulceration [1951], p. 330
Hormonal overaction in relation to gastric secretion in chronic duodenal ulcer [1951], p. 330
Banthine in the treatment of peptic ulcer [1951], p. 330
Medical and surgical treatment of cases of peptic ulcer with gross bleeding [1951], p. 331
Surgical treatment of intractable duodenal ulceration [1951], p. 331
Bilateral transpleural vagotomy with vagus resection [1951], p. 332
Gastroscopic and histological appearances before and after vagotomy [1951], p. 332
Results of vagotomy in peptic ulcer [1951], p. 332
Partial gastrectomy for peptic ulcer [1951], p. 333
Subtotal gastric resection and bilateral vagotomy for gastric and duodenal ulcers [1951], p. 333
Post-operative mortality and methods of partial gastrectomy [1951], p. 334
Necropsy findings, innocent and malignant [1952], p. 257
Medical and surgical treatment in general practice [1952], p. 257
Surgical treatment for duodenal ulcer [1952], p. 258
Gastric resection for duodenal ulcer [1952], p. 258
Late results of resection for gastro-duodenal ulcer [1952], p. 258
Gastrectomy: post-operative syndromes [1952], p. 259

Vol. 6

KEY NO.

262 PEPTIC ULCER AND ITS COMPLICATIONS (*cont.*):

Abstracts (cont.):

Vol. 6

KEY NO.

262 PEPTIC ULCER AND ITS COMPLICATIONS (*cont.*):

Abstracts (cont.):

Bleeding duodenal ulcer: vagotomy and pyloroplasty: follow-up study [1959], p. 72
Gastrojejunal ulcer: radiographic examination [1959], p. 73
Anastomotic ulcer: management [1959], p. 73
Postgastrectomy patients: psychiatric observations [1960], p. 103
Gastro-duodenal ulcers: necropsy analysis with emphasis on associated endocrine disease [1960], p. 314

263 PERFORATING ULCER OF THE FOOT

No further references

264 PERITONEUM AND PERITONITIS

Articles

Appendicitis and peritonitis [1951], p. 32
Cytology in the diagnosis of cancer of the alimentary tract [1957], p. 66
Ascites [1957], p. 68

Abstracts

Ascites: diagnosis [1955], p. 288
Biopsy specimens: Ruddock peritoneoscope and modified forceps [1955], p. 289
Primary retroperitoneal tumours: incidence of specific types [1955], p. 289
Acute chylous peritonitis: clinical appearances and treatment [1956], p. 307

Vol. 7

265 PHARYNGEAL DIVERTICULA

Abstracts

Mechanism of herniation [1951], p. 334
Pharyngo-oesophageal diverticulosis: surgical treatment [1953], p. 309
Pharyngeal diverticula: treatment [1957], p. 319

266 PHYSIOTHERAPY

Abstract

Electromyography in orthopaedics [1951], p. 335

267 PHYSIQUE, BODY BUILD AND POSTURE

No further references

Vol. 7

KEY NO.

New Heading **PITUITARY GLAND**

Article

Progress in endocrine surgery [1957], p. 137
Pituitary [1957], p. 155

Abstracts

Pituitary destruction in advanced cancer: radon implants [1957], p. 176
Pituitary adenoma: treatment [1958], p. 342
Screw-implantation of the pituitary: yttrium-90 (1959), p. 269

268 **PITUITARY TUMOURS**

Abstract

Treatment: ACTH in conjunction with surgery [1955], p. 289

269 **PLASTIC SURGERY—CORNEAL GRAFTING**

Abstracts

Scope of corneal grafting [1954], p. 277
Partial penetrating keratoplasty [1954], p. 278
Collection and preservation of graft [1954], p. 278
Use of special punch in corneal grafting: technique [1955], p. 290

New Heading **PLASTIC SURGERY—CORRECTION OF FACIAL DEFORMITY**

Article

Plastic procedures [1956], p. 72
The Abbe operation [1956], p. 72
The bat or winged ear deformity [1956], p. 75
Rhinophyma [1956], p. 79
Saddle nose [1956], p. 79

270-273 **PLEURA—DISEASES OF**

Articles

Biological decortication (enzyme debridement) [1953], p. 235
Progress in pulmonary surgery [1958], p. 152
Empyema [1958], p. 156

Abstracts

Pleural cysts: development and treatment [1952], p. 263
Chronic pleural empyema: treatment [1956], p. 307
Recurrent spontaneous pneumothorax: parietal pleurectomy [1957], p. 107
Decortication of the lungs: indications and results [1957], p. 108

274 **POLIOMYELITIS**

Articles

Poliomyelitis [1954], p. 147
Poliomyelitis: the distribution of the paralysis [1956], p. 83
Muscle paralysis in the acute and convalescent stages [1956], p. 83
Clinical distribution of the permanent paralysis [1956], p. 86

Vol. 7

KEY NO.

274 POLIOMYELITIS (*cont.*):

Articles (cont.):

Poliomyelitis: the distribution of the paralysis (*cont.*):
- Patterns of paralysis in the lower limb [1956], p. 89
- The pathological basis of the muscle paralysis [1956], p. 94
- Segmental innervation in relation to affection or paralysis of muscles [1956], p. 94
- The spinal cord in the normal and poliomyelitis [1956], p. 95
- The practical application of these findings [1956], p. 101

Abstracts

Muscle recovery: tests on 149 patients suffering from paralytic poliomyelitis [1955], p. 290
Abductor paralysis of shoulder: value of splinting [1956], p. 305
Poliomyelitis vaccination [1960], p. 378
Poliomyelitis: transportation of severely paralysed patients [1960], p. 379
Assessment of respiratory failure [1960], p. 379

275 POLYCYSTIC DISEASE

Article

Pulmonary cysts [1957], p. 92
- Epithelial cysts [1957], p. 93
- Emphysematous cysts [1957], p. 94
- Emphysematous cysts in infancy [1957], p. 98

Abstracts

Unilateral polycystic kidney disease [1951], p. 335
Renal lesions in the child: aetiology [1952], p. 263

276 POST-OPERATIVE GANGRENE

No further references

277 PREGNANCY—SURGICAL INTERVENTION DURING

Articles

Carcinoma of the cervix in pregnancy [1957], p. 218
Rupture of the gravid uterus [1957], p. 229
Surgical induction of labour [1958], p. 205
- Incidence [1958], p. 205
- Technique [1958], p. 205
- Risk of surgical induction [1958], p. 208
- Effectiveness of surgical induction [1958], p. 210
- Indications [1958], p. 215

Vol. 7

KEY NO.

Vol. 7

KEY NO.

279 PROTRACTED ILLNESS—MANAGEMENT AND REHABILITATION

No further references

280 PULMONARY ABSCESS

No further references

281 PULMONARY TUBERCULOSIS

Article

Lung resection for pulmonary tuberculosis [1957], p. 82
- Indications for resection [1957], p. 84
- Pre-operative preparation [1957], p. 86
- Anaesthesia [1957], p. 86
- Post-operative period [1957], p. 87
- Post-operative complications [1957], p. 87
- Results of resection [1957], p. 88

Abstracts

Standard lung dissection operations in children [1952], p. 267
Late results of thoracoplasty [1952], p. 267
Pneumonectomy and immediate thoracoplasty: technique [1953], p. 311
Development of haemothorax following artificial pneumothorax refill [1953], p. 311
Treatment: age considerations in relation to thoracoplasty [1955], p. 293
Segmental and wedge resection; lobectomy and pneumonectomy in treatment of pulmonary tuberculosis [1956], p. 310
Conservative resection of bronchial tree: review of methods [1957], p. 108
Pulmonary tuberculosis: timed vital capacity and maximal breathing capacity [1957], p. 109

282 PYLEPHLEBITIS

No further references

283 PYLORIC STENOSIS OF INFANTS

Abstract

Theory of post-natal development [1952], p. 268

284 RABIES

No further references

285 RADIOACTIVE ISOTOPES

Articles

Clinical uses of radioactive isotopes [1951], p. 237
Progress in the clinical use of radioactive isotopes [1959], p. 347
- Diagnostic applications [1959], p. 348
- Therapy [1959], p. 351
- Physics and techniques [1959], p. 363
- Hazards of radiation [1959], p. 365

Vol. 7

KEY NO.

285 RADIOACTIVE ISOTOPES (*cont.*):

Abstracts

Radioactive phosphorus in determining limits of spread of cerebral gliomas [1951], p. 285
Red-cell loss from gastro-intestinal tract: measurement of radioactive chromium [1959], p. 375
Intraocular tumours: detection with radioactive phosphorus [1959], p. 375
Heidelberg techniques of contact irradiation with cobalt 60 [1959], p. 377
Epidermoid carcinoma: effect of cobalt 60 beam therapy [1959], p. 378

286 RADIOTHERAPY

Article

Carcinoma of the larynx [1957], p. 310

Abstracts

Bone tumours [1954], p. 280
30 meV synchroton [1954], p. 280
Radiation sickness: treatment [1955], p. 294
Pituitary destruction in advanced cancer: radon implants [1957], p. 176

287-288 RECONSTRUCTION OF THE EAR AND NOSE

Abstract

Rhinoplastic reconstruction: the role of the septum [1951], p. 340

289 RECTUM—BENIGN TUMOURS OF

Abstracts

Diffuse familial polyposis of the colon [1952], p. 269
Villous tumours: radical approach in treatment [1956], p. 311
Familial polyposis: review of major surgical treatment [1957], p. 74

290 RECTUM—CARCINOMA OF

Articles

Restorative resection of the rectum [1952], p. 87
Radical surgical treatment of carcinoma of the rectum [1959], p. 91
Combined excision [1959], p. 91
Sphincter-saving resections [1959], p. 94
Results of surgical treatment [1959], p. 98

Vol. 7

KEY NO.

290 RECTUM—CARCINOMA OF (*cont.*):

Abstracts

Perineal dissection in excision [1952], p. 269
Excision combined with colostomy: post-operative obstruction of the small intestine [1952], p. 269
Treatment: radical surgery and radiotherapy [1954], p. 280
Submucosal rectal carcinoids: incidence and treatment [1955], p. 294
Carcinoma of rectum: anterior resection [1959], p. 101
Carcinoma of rectum and rectosigmoid: survival after anterior resection [1959], p. 102
Carcinoma of mid and upper parts of rectum: abdomino-endorectal resection [1959], p. 102
Carcinoma of rectum and colon: implantation recurrence [1959], p. 102
Carcinoid tumours of the rectum: clinical study [1960], p. 102

291 RECTUM—HAEMORRHOIDS

Article

Internal haemorrhoids [1959], p. 85
A new technique for submucosal haemorrhoidectomy with high ligation [1959], p. 85

Abstracts

Haemorrhoidectomy [1954], p. 281
Haemorrhoids: anatomy of anal canal [1957], p. 77

292 RECTUM—PROCTITIS

No further references

293 RECTUM—PROLAPSE

Articles

The treatment of rectal prolapse [1956], p. 104
Partial prolapse [1956], p. 104
Complete rectal prolapse [1956], p. 105
Abdominal operations for rectal prolapse [1956], p. 110
Complete prolapse of the rectum [1959], p. 86
Anterior resection [1959], p. 87
The modified Roscoe Graham or Dunphy type of repair [1959], p. 87
Rectal function after operations for complete prolapse [1959], p. 90
Palliative treatment of complete prolapse by Thiersch operation [1959], p. 91

Abstracts

Treatment for massive prolapse [1953], p. 312
Oil-soluble anaesthetics and lasting analgesia [1953], p. 312
Treatment: surgical treatment [1954], p. 281
Prolapse of rectum: mechanism and treatment [1957], p. 77

Vol. 7

KEY NO.

294 REFRIGERATION ANAESTHESIA

Article

Hypothermic anaesthesia [1956], p. 177
- Cardiovascular surgery [1956], p. 177
- Neurosurgery [1956], p. 178
- Aortic grafting procedures [1956], p. 178
- *The advantages accruing from the hypothermic state [1956], p. 178*
- Methods of inducing hypothermia [1956], p. 184

295 RESUSCITATION

No further references

296 RETINA

Articles

Retinal detachment: improvements in investigation and treatment [1953], p. 224

Modern methods of treating retinal detachments [1960], p. 316
- Diathermy [1960], p. 317
- Lamellar scleral resection [1960], p. 318
- The vitreous implant [1960], p. 322
- Light coagulation [1960], p. 327
- Prophylactic treatment of retinal detachments [1960], p. 331

Abstracts

Diathermy and antibiotics in simple detachment [1952], p. 270
Medical detachments of the retina [1960], p. 335
Traumatic retinal detachments and myopia [1960], p. 336
Retinal separation: exudative type [1960], p. 336
Elevation of choroid by insertion of polyvinyl sponge: an experimental study [1960], p. 337
Scleral imbrication [1960], p. 337
Scleral buckling operation: use of accessory instrumentation [1960], p. 338
Scleral buckling operation with rolled scleral flap [1960], p. 338
Use of fixation pick and scleral depressor [1960], p. 338
Drainage of subretinal fluid [1906], p. 339
Re-operation after diathermy or scleral resection: difficulties encountered [1960], p. 339
Retinal detachment surgery: results [1960], p. 340

297 SACRO-COCCYGEAL REGION—SURGERY OF

Abstract

Sacro-coccygeal pilonidal cyst *[1951]*, p. 342

298 SALIVARY GLANDS

Articles

Salivary glands—parotitis [1956], p. 115
- Infective parotitis [1956], p. 115
- Parotitis secondary to calculus formation [1956], p. 118
- Recurrent or chronic parotitis of obscure origin [1956], p. 118

Vol. 7

KEY NO.

298 SALIVARY GLANDS (*cont.*):

Articles (cont.):

The problem of recurrence and malignancy in tumours of the parotid [1959], p. 104

The present position of parotid surgery [1959], p. 105

Material [1959], p. 105

Recurrent mixed tumours [1959], p. 105

Cylindroma [1959], p. 109

Muco-epidermoid tumour [1959], p. 110

Carcinoma [1959], p. 112

Some points in the surgical treatment of recurrent and malignant parotid tumours [1959], p. 117

The possibility of improvement in results [1959], p. 119

Abstracts

Functions of the parotid gland [1951], p. 342

Results of radiation therapy in parotid tumours [1951], p. 343

Repair of lacerated parotid duct [1951], p. 343

Parotid gland: fatty infiltration simulating mixed tumour [1956], p. 311

Sialoangiectasis of the parotid glands [1956], p. 312

Acute suppurative parotitis: treatment [1956], p. 312

Diagnosis and management [1959], p. 120

Pathology and treatment [1959], p. 121

Recurrent mixed tumours of the major salivary glands: management *[1959], p. 122*

Chronic or recurrent sialadenitis: parotidectomy [1959], p. 122

Salivary gland virus disease [1960], p. 383

299 SCALP AND SKULL

No further reference

300 SCHISTOSOMIASIS

No further references

301 SCIATICA

No further references

302 SCLERA

No further references

303 SCURVY—MASKED AND MANIFEST

No further references

304 SKIN—DISEASES OF, IN RELATION TO SURGERY

Abstracts

Pilonidal disease: diagnosis and treatment [1955], p. 295

Staphylococcal skin infections: infrequency of satisfactory cure [1955], p. 295

Vol. 7

KEY NO.

305 SPEECH THERAPY

No further references

306 SPINAL COLUMN

Articles

Abstracts

307 SPINAL CORD

Articles

Vol. 7

KEY NO.

307 SPINAL CORD (*cont.*):

Articles (cont.):

Surgery of the spinal cord (*cont.*):
- Calcified herniated disc in a child [1958], p. 315
- Rarer cord lesions [1958], p. 315
- *Flexion spasms and contractures in disease of the spinal cord [1958],* p. 316

Micturition disorders associated with spina bifida [*1960*], p. 341
- Congenital spinal palsy [1960], p. 341
- Assessment of methods of treatment [1960], p. 349
- Investigations [1960], p. 350
- Treatment [1960], p. 353

Abstracts

Compression paraplegia: rare causes and treatment by laminectomy [*1952*], p. 272
Lumbar and sacral cysts [1952], p. 273
Surgical treatment of pain [1952], p. 273
Intramedullary lipoma [1954], p. 282
Pott's paraplegia: treatment [1955], p. 298
Myelocele and meningomyelocele: follow-up of 5 cases [1955], p. 298
Spinal canal: dilatation at thoraco-lumbar junction [1956], p. 313
Tumours: compression of spinal cord [1956], p. 313

Vol. 8

308 SPLEEN—SURGERY OF

Abstracts

Indications for porta-caval shunt in splenic anaemia [*1952*], p. *274*
Porta-caval, spleno-renal and other venous shunts in splenic anaemia [1952], p. 274
Kala-azar: effects and treatment by splenectomy [1952], p. 274
Diagnostic radiology in visualization of splenic and portal circulation [1953], p. 313
Malignant tumour of the spleen [1953], p. 313
Banti's syndrome: diagnosis [1953], p. 313
Essential thrombocytopenic purpura: treatment by splenectomy [1953], p. 314
Splenectomy: indications and technique [1953], p. 314
Splenectomy: anatomical and physiological considerations [1953], p. 314
Banti's disease: portal venography in the demonstration of veins suitable for anastomosis [1955], p. 299
Aneurysm of the splenic artery: resection [1955], p. 299
Splenectomy: indications and results [1956], p. 314
Rupture of the spleen: radiological diagnosis and treatment [1956], p. 314

309-310 STERILITY AND STERILIZATION

No further references

Vol. 8

KEY NO.

311 STERILIZATION OF SURGICAL APPARATUS

Article

Sterilization by heat [1959], p. 1
Sterilization by steam under pressure [1959], p. 1
Sterilization by dry heat [1959], p. 10

Abstracts

Sterilization of operating-room by means of antibiotics [1951], p. 348
Bactericides: benzchlorophenol [1952], p. 275
Sterilizers [1959], p. 12
Automatically controlled, high prevacuum sterilizer [1959], p. 13
Testing of sterilizers [1959], p. 13
Thermal death-times of spores in dry heat [1959], p. 14

312 STOMACH—DISEASES OF

Articles

Carcinoma of the stomach *[1954], p. 232*
Anaemias following gastro-intestinal operation [1957], p. 63
Hypochromic anaemia after partial gastrectomy [1957], p. 63
Role of hydrochloric acid [1957], p. 63
Studies in iron balance [1957], p. 64
Blood loss [1957], p. 64
Anaemia due to deficient intake [1957], p. 64
Megaloblastic anaemias after operation [1957], p. 64
Cytology in the diagnosis of cancer of the alimentary tract [1957], p. 66
The stomach and duodenum [1958], p. 62
ABO blood groups [1958], p. 62
Acute pancreatitis following gastrectomy [1958], p. 63
Perforated peptic ulcer [1958], p. 64
Gastro-duodenal haemorrhage [1958], p. 66

Abstracts

Indications for gastrectomy and for vagotomy [1951], p. 348
Gastro-intestinal lymphosarcoma [1951], p. 349
Gastric obstruction resulting from the swallowing of corrosive poison [1952], p. 275
Tumours: surgical methods of treatment [1953], p. 315
Clinical history of carcinoma and results of resection [1953], p. 315
Gastric operations [1954], p. 282
Gastric polyposis [1954], p. 283
Mucosal hypertrophy [1954], p. 284
Partial gastrectomy: complications [1956], p. 315
Benign gastric tumours: diagnosis [1956], p. 315
Pyloric hypertrophy in adults: laparotomy finding [1957], p. 71
Carcinoma of the stomach: ABO blood group [1958], p. 119
Lymphatic spread of gastric cancer [1958], p. 120
Total gastrectomy [1958], p. 120
Gastric ulcer: modified Billroth II and incidence of carcinoma [1958], p. 121
Peptic ulcer: acute perforation [1958], p. 121

KEY NO.

312 STOMACH—DISEASES OF (*cont.*):

Abstracts (*cont.*):

Peptic ulcer: haemorrhage [1958], p. 122
Billroth I and Billroth II [1958], p. 122
Partial gastrectomy [1958], p. 123
Postgastrectomy dumping syndrome: pathogenesis [1958], p. 123
Postgastrectomy dumping syndrome: complication of Billroth II for peptic ulcer [1958], p. 124
Complications of gastrectomy: complications associated with long afferent loop of Polya operation [1958], p. 124
Complications of gastrectomy: haemorrhage [1958], p. 125
Unusual complications of subtotal gastrectomy [1958], p. 125
Pulmonary tuberculosis following gastric resection [1958], p. 126

313 STRABISMUS AND HETEROPHORIA

Abstract

Esophoria: surgical treatment [1952], p. 276

STRESS INCONTINENCE, *see* Pelvic Organs

314 SUBPHRENIC ABSCESS

Abstracts

Anatomy, clinical picture, diagnosis and treatment of subphrenic abscess [1951], p. 349
Incidence and treatment of subphrenic abscess [1951], p. 350
Spread of infection to chest [1956], p. 315

315 SUPRASPINATUS LESIONS

No further references

316 SURGICAL TECHNIQUE

Abstracts

Control of the circulation with hypotensive drugs and by posture [1951], p. 350
Fortisan as a suture material [1951], p. 351
Use of cortisone and ACTH: effect on healing [1953], p. 316

317 SURGICAL TECHNIQUE—WOUND DRESSINGS

Article

Staphylococcal infection in hospital [1957], p. 41
Infection in the operating theatre [1957], p. 43
Infection in the ward [1957], p. 47
Chemotherapy [1957], p. 48
Strains of staphylococcus aureus [1957], p. 49
Methods of control of staphylococcal spread [1957], p. 51
Other factors in wound infection [1957], p. 53

Abstract

Staphylococcal infections: current problems [1957], p. 56

Vol. 8

KEY NO.

318 SYPHILIS

No further references

319 TABES DORSALIS (LOCOMOTOR ATAXIA)

Abstract

Treatment: results of surgical intervention [1954], p. 284

320 TESTICLE AND TUNICA VAGINALIS

Abstracts

Histology of testicular tissues and tumours and isolation of ketosteroids [1952], p. 276
Cholesteatoma of epididymis [1952], p. 277
Radiotherapy after orchidectomy [1952], p. 277
Tumours of spermatic cord: primary or secondary [1952], p. 277
Epididymis: sarcoma [1954], p. 273
Germinal tumour of the testis: relationship of interstitial cell hyperplasia to urinary gonadotrophins, testicular atrophy and histological type [1955], p. 299
Imperfect descent of the testis: treatment [1955], p. 300
Tumour of the vas deferens: clinical findings [1955], p. 300
Primary carcinoma of the epididymis: diagnosis and treatment [1955], p. 301
Tuberculous epididymitis: treatment [1955], p. 301
Metaplasia: pathology [1955], p. 301
Adenocarcinoma of the excretory ducts: occurrence in maldescended testicle [1955], p. 302
Epididymitis: combined therapy [1956], p. 316
Imperfect descent of the testicle [1956], p. 316

321 TETANUS

Abstracts

Immunization: duration of vaccine immunity [1955], p. 302
Treatment: tracheotomy and positive pressure ventilation [1955], p. 303

322 TETANY

Abstract

Relation to potassium deficiency: experimental observations [1955], p. 303

323 THORACIC AND INTRATHORACIC INJURIES

Abstracts

Studies on normal anatomy of bronchial arteries [1952], p. 278
Tantalum gauze in repair of large gunshot wound [1952], p. 278
Atelectasis: prevention and treatment [1952], p. 278
Angiocardiography, intrathoracic, to display foreign bodies [1952], p. 279
Injuries to the parietes: method of reuniting ribs [1953], p. 317
Crush injuries of the chest: surgical management [1955], p. 304
Chest wall defects: prosthetic repair [1957], p. 111
Chest injury: rupture of bronchus [1957], p. 112

Vol. 8

KEY NO.

New Heading **THORAX—CONGENITAL DEFORMITIES**

Article

Thorax—congenital deformities [1956], p. 150
- Funnel chest (pectus excavatum) [1956], p. 150
- Deficiencies of the chest wall [1956], p. 160

324 THROMBOSIS AND EMBOLISM

Abstracts

Emotions in relation to clotting time and viscosity of blood [1952], p. 279
Thrombosis of renal vein in an infant [1952], p. 279
Insidious thrombosis of the abdominal aorta [1952], p. 280
Ilio-femoral thrombophlebitis: causes and treatment *[1952]*, p. *280*
Aorta: embolectomy [1952], p. 280
Thrombophlebitis migrans: treatment [1955], p. 304
Thrombosis of the common carotid artery [1955], p. 305
Embolism: progress in management [1955], p. 305
Thrombosis in malignant disease [1956], p. 317
Serotonin and pulmonary embolism: experimental studies [1960], p. 102
Prevention of venous thrombosis and pulmonary embolism: trial of anticoagulant prophylaxis in fracture cases [1960], p. 129

325 THYMUS GLAND

Article

Thymus [1957], p. 156

Abstracts

Thymectomy: indications and assessment of results [1951], p. 353
Radiographic procedures in diagnosis of tumours [1953], p. 317
Myasthenia gravis associated with myopathy: thymectomy [1957], p. 176

326 THYROGLOSSAL CYST, SINUS AND FISTULA

No further references

327 THYROID GLAND—DISEASES OF

Articles

Thyroiditis [1955], p. 148
The thyroid [1957], p. 137
- Hashimoto's thyroiditis [1957], p. 137
- Nodular goitre [1957], p. 139
- Mediastinal goitre [1957], p. 142
- Hyperthyroidism [1957], p. 143
- Thyroid cancer [1957], p. 146
- Exophthalmos [1957], p. 149

Vol. 8

KEY NO.

327 THYROID GLAND—DISEASES OF (*cont.*):

Articles (cont.):

The thyroid gland [1959], p. 123
- Endemic goitre [1959], p. 123
- The thyroid nodule [1959], p. 124
- Congenital deafness associated with goitre [1959], p. 125
- Cretins [1959], p. 125
- Thyroiditis [1959], p. 126
- Cancer of the thyroid [1959], p. 127
- Exophthalmos [1959], p. 129

Abstracts

- Lateral aberrant cancer [1952], p. 281
- Posterior mediastinal goitre [1952], p. 281
- Thyroiditis: needle biopsy in differential diagnosis [1952], p. 282
- Diagnosis with radioactive iodine [1952], p. 282
- Types of thyrotoxicosis and their management [1952], p. 282
- Use of thiouracil in increasing uptake of radio-iodine absorption [1952], p. 283
- Radio-iodine in the treatment of carcinoma [1952], p. 283
- Radioactive iodine as an adjunct to surgery [1952], p. 284
- Operative technique: adequate and inadequate operations [1942], p. 284
- Regeneration of human thyroid after thyroidectomy [1952], p. 284
- Radioactive iodine tracer studies after thyroidectomy [1952], p. 285
- Aetiology [1954], p. 284
- Treatment [1954], p. 285
- Adenoma and carcinoma [1954], p. 286
- Carcinoma of the thyroid: classification and review of 190 cases [1955], p. 305
- Crico-thyroid syndrome: surgical treatment [1955], p. 306
- Thyroid neoplasms: relation to Hashimoto's disease [1955], p. 306
- Malignant tumours: relationship of lymphosarcoma and Hashimoto disease [1956], p. 317
- Carcinoma of the thyroid in children: treatment [1956], p. 318
- Conservative operations for malignant tumours: results [1956], p. 318
- Treatment of metastatic carcinoma with radio-iodine [1956], p. 319
- Thyroid gland disorders [1957], p. 156
- Thyroiditis: diagnosis and treatment [1957], p. 157
- Hashimoto's disease: auto-antibodies [1957], p. 157
- Diagnostic and biochemical aspects [1957], p. 158
- Needle biopsy of the thyroid gland: technique and results [1957], p. 158
- Thyroid adenomas: genesis [1957], p. 159
- Clinical signs [1957], p. 159
- Nodular goitre: genesis and management [1957], p. 159
- Nature and treatment in children [1957], p. 160
- Indications for treatment [1957], p. 161
- Recurrent goitre: management [1957], p. 161
- Mediastinal goitre: origin by descent from the neck [1957], p. 162
- Squamous cell cysts of thyroid gland: origin of cells [1957], p. 162
- Thyrotoxicosis: diagnosis and treatment [1957], p. 163

Vol. 8

KEY NO.

327 THYROID GLAND—DISEASES OF (*cont.*):

Abstracts (cont.):

Antithyroid drugs [1957], p. 163
Management [1957], p. 164
Management in children [1957], p. 165
Treatment with radio-iodine [1957], p. 165
Surgery of the thyroid gland: mortality rate and causes of death [1957], p. 166
Thyroid gland auto-implants in rats: survival time and reaction to methylthiouracil [1957], p. 166
Thyroid tumours: aetiology and management [1957], p. 167
Thyroid cancer: clinico-pathological study [1957], p. 167
Hürthle-cell tumours of the thyroid gland [1957], p. 168
Experimental induction, surgical treatment and radiotherapy [1957], p. 168
Papillary tumours [1957], p. 169
Carcinoma of the thyroid gland in children: pathology and treatment [1957], p. 170
Study of case histories [1957], p. 170
Metastatic carcinoma of the thyroid: management with radioactive iodine [1957], p. 171
Exophthalmos: report of case with persistent lactation [1957], p. 171
A method of orbital decompression [1957], p. 172
Recurrent laryngeal nerves: injury during thyroidectomy [1957], p. 320
The thyroid nodule: autoradiographic studies [1959], p. 133
Triiodothyronine: clinical applications [1959], p. 133
Subacute thyroiditis: mumps virus [1959], p. 134
Riedel's struma [1959], p. 134
Thyroid cancer [1959], p. 134
Dependency [1959], p. 135
Small-cell malignant lesions [1959], p. 135
Thyroid function: mammary cancer [1959], p. 269

328 TONSILLITIS

No further references

329 TROPICAL DISEASE—SURGERY IN

Abstract

Treatment of ulcers [1952], p. 285

330 TUBERCULOSIS

Articles

Tuberculosis of the endometrium [1957], p. 227
Urinary tuberculosis [1960], p. 164
- General principles of modern therapy [1960], p. 165
- Antituberculous drugs [1960], p. 166
- Ambulatory treatment [1960], p. 166
- Urine examinations [1960], p. 167
- Institutional versus ambulatory treatment [1960], p. 167

Vol. 8

KEY NO.

330 **TUBERCULOSIS** (*cont.*):

Articles (cont.):

Urinary tuberculosis (*cont.*):
Indications for surgery [1960], p. 168
The calyx [1960], p. 168
The pelvi-ureteric junction [1960], p. 174
Lower ureteric obstruction [1960], p. 174
The systolic bladder [1960], p. 179
Urinary diversion [1960], p. 183

Abstracts

Comparative merits of measures for detecting the tubercle bacillus [1951], p. 355
The Mantoux tuberculin test in diagnosis: negative reactions [1951], p. 355
Streptomycin treatment in genito-peritoneal tuberculosis [1951], p. 355

331 **TYPHOID FEVER—SURGERY IN**

No further references

332 **ULCERS AND ULCERATION**

Abstract

Rodent ulcer of neck, trunk and limbs [1951], p. 356

333 **UMBILICUS—DISEASES OF**

No further references

334 **URAEMIA**

Article

Anuria [1957], p. 262

Abstracts

Management of anuria [1951], p. 356
Peritoneal lavage in acute anuria [1951], p. 357
Peritoneal irrigation in an infant with oliguria due to ascending suppurative pyelonephritis [1951], p. 357
The artificial kidney [1951], p. 358
A new type of artificial kidney [1952], p. 286
Acute anuria: management [1957], p. 280
Post-nephrectomy renal failure: case report [1957], p. 280

New Heading **URETER—REPLACEMENT OF**

Abstracts

Total replacement of ureter [1958], p. 264
Ureteral substitution by isolated ileal loop [1958], p. 265
Ureteral substitute: uroepithelial lined small bowel [1960], p. 364

Vol. 8

KEY NO.

335 URETER—TRANSPLANTATION OF

Articles

Abstracts

336 URETHRA AND BLADDER—CONGENITAL MALFORMATIONS

Abstracts

337 URETHRA—NEW GROWTHS AND STRICTURE

Abstracts

Vol. 8

KEY NO.

Vol. 8

KEY NO.

341 UTERUS—CERVIX; AND VAGINA (*cont.*):

Abstracts

342 UVEAL TRACT

No further references

343 VASCULAR SURGERY

Articles

Abstracts

Vol. 8

KEY NO.

343 VASCULAR SURGERY (*cont.*):

Abstracts (cont.):

Pulmonary stenosis: kymography and catheterization [1952], p. 290
Commissurotomy in mitral stenosis [1952], p. 291
Finger-fracture valvuloplasty in mitral stenosis [1952], p. 291
Results of commissurotomy [1952], p. 291
Valvulotomy in mitral valve disease [1953], p. 318
Patent ductus arteriosus: diagnosis [1953], p. 318
Patent ductus arteriosus: indication for treatment, technique and results [1953], p. 319
Aortic diseases [1954], p. 287
Coronary disease [1954], p. 288
Venous thrombosis [1954], p. 288
Mitral valvular disease: surgical treatment [1955], p. 312
Human aortic homografts for arteriosclerotic aneurysms and thrombo-obliterative disease: structural changes [1955], p. 312
Aortic stenosis: treatment [1955], p. 313
Thrombo-obliterative disease of the aorta: surgical treatment [1955], p. 313
Acquired tricuspid stenosis: clinical diagnosis and treatment [1956], p. 322
Atrial septal defects: operative repair under direct vision [1956], p. 322
Coarctation of the aorta: criteria for surgical treatment [1956], p. 323
Tetralogy of Fallot: treatment [1956], p. 323
Intracardiac surgery: pre-operative assessment and post-operative management [1956], p. 323
Congenital heart disease: creation of pulmonary artery stenosis in cases with pulmonary hypertension [1957], p. 332
Atrial septal defect [1957], p. 332
Analysis of causes of death following operation [1957], p. 333
Mitral commissurotomy: analysis of results [1957], p. 333
Extracorporeal circulation: Gibbon-type pump-oxygenator [1957], p. 334
Molar sodium lactate: effect in cardiac surgery [1957], p. 334
Cardiac arrest and resuscitation [1957], p. 348
Hypothermia [1957], p. 350
Surface cooling for use in open heart surgery [1957], p. 350
Veno-venous cooling [1957], p. 351
Application to surgery [1957], p. 351
Cardiac effects of hypotensive drugs and muscle relaxants [1957], p. 352
Peripheral vascular grafts: experimental comparisons [1960], p. 51
Abdominal aortic aneurysm: results of treatment by resectional placement of homograft [1960], p. 54
Coarctation of the abdominal aorta [1960], p. 55
Surgical treatment of mitral stenosis: transventricular approach with mechanical dilator [1960], p. 158
Pulmonary stenosis: valvotomy [1960], p. 159
Atrial septal defect, secundum: open surgical repair [1960], p. 159
Anomalous pulmonary venous drainage [1960], p. 160
Simultaneous repair of mitral and tricuspid valves [1960], p. 160

Vol. 8

KEY NO.

343 VASCULAR SURGERY (*cont.*):

344 VEINS—VARICOSE

New Heading VIRUS DISEASES

Vol. 8

KEY NO.

345 VISCEROPTOSIS

No further references

346 VISUAL FIELDS—PERIMETRY AND INTERPRETATION

No further references

347 VITAMINS AND NUTRITION IN RELATION TO SURGERY

Abstracts

Fat supplements [1954], p. 289
Malnutrition in surgical patients: treatment [1955], p. 314

348 VITREOUS—INJURIES AND DISEASES

No further references

349 VOLVULUS

No further references

350 YAWS

Article

Yaws—Skeletal manifestations [1955], p. 136

Abstract

Antibiotic therapy [1952], p. 292